PL1

Ateroskleroza

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Ateroskleroza je upalni fibroproliferativni proces u kojem sudjeluju stanice stijenke krvne žile, poglavito endotelne i glatke mišićne stanice te leukociti-monociti i T-limfociti, ali i trombociti s tvarima koje proizvode, a koje potiču međusobnu aktivnost i oštećenja stanica. Zbog toga dolazi do lokalnog zadebljanja stijenke arterije koje se naziva aterom ili plak (francuski plaque - ploča, jer na stijenci žile aterosklerotične naslage često izgledaju kao masne ploče). Aterom se sastoji od meke, kašaste jezgre građene iz lipida, poglavito kolesterola i raspadnutih stanica, koju prekriva "kapa" sastavljena od izmijenjenih glatkih mišićnih stanica i veziva, poglavito kolagena, elastina i mukopolisaharida. Danas se smatra da aterogeneza započinje poremećajem funkcije endotela uzrokovanim čimbenicima rizika kao što su hiperkolesterolemija, pušenje, hipertenzija, hiperhomocisteinemija i poremećen metabolizam glukoze. U sklopu poremećaja funkcije endotela dolazi do povećane propusnosti endotela za serumske lipoproteine i ostale sastojke plazme, što je posredovano pomoću NO, PDGF, prostaciklinom, angiotenzinom-II i endotelinom. Također zbog aktivacije NF-kB dolazi do očitovanja adhezijskih molekula na endotelnim stanicama uključujući VCAM-1, ICAM-1 i selektine te do migracije leukocita i monocita/makrofaga u subendotelni prostor, što je pak posredovano oksidiranim LDL, MCP-1, PDGF i MCSF. Nakon toga dolazi do migracije glatkih mišićnih stanica iz medije krvne žile u intimu i njihovog umnožavanja (to potiču PDGF i TGF-beta), aktivacije T-stanica (to potiču TNF-alfa i IL-2), pretvaranja makrofaga pretrpanih lipidima u tzv. "pjenaste stanice" (to potiču oksidirani LDL, MCSF, TNF-alfa i IL-1) i nakupljanja trombocita, što pak potiču čimbenici kao što su tromboksan A2, tkivni čimbenik i drugi. Nakupljanje trombocita potiče i to što hiperlipidemija, a osobito hipertrigliceridemija, potiče sintezu PAI-1 u endotelnim stanicama, a on igra važnu ulogu u aterogenezi, jer smanjuje fibrinolitičku aktivnost i potiče trombogenezu. Glatke mišićne stanice stvaraju vezivnu kapu preko lipidne jezgre ateroma koja odvaja lipidnu jezgru od lumena krvne žile i krvi. Niz čimbenika, od kojih je najvažniji sastav ateroma, utječe na to hoće li aterom ostati stabilan ili će njegova kapa puknuti, pričem dolazi do stvaranja tromba na tom mjestu. Do pucanja kape ateroma poglavito dolazi zbog aktivacije makrofaga (pod utjecajem upalnih stanica, osobito T-limofocita) koji luče kovinoproteinaze (kolagenaze, elastaze) i druge

PL1

Atherosclerosis

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Atherosclerosis is an inflammatory fibroproliferative process involving vascular wall cells, especially endothelial and smooth muscle cells, leukocytes-monocytes and T lymphocytes as well as platelets with the substances they produce, which stimulate cellular interactivity and damage. This leads to local arterial wall thickening known as atheroma or plaque (Fr. *plaque*, flat area, because atherosclerotic deposits on vascular wall frequently look like adipose plates). Atheroma consists of a soft, pulpy core made of lipids, mainly cholesterol, and degraded cells, covered with a "cap" consisting of altered smooth muscle cells and connective tissue, mainly collagen, elastin and mucopolysaccharides. It is currently considered that atherogenesis begins with endothelial function impairment caused by risk factors such as hypercholesterolemia, smoking, hypertension, hyperhomocysteinemia and impaired glucose metabolism. The endothelial functional impairment includes increased endothelial permeability for serum lipoproteins and other plasma components, which is mediated by NO, PDGF, prostacyclin, angiotensin-II and endothelin. The activation of NF-κB entails expression of adhesion molecules including VCAM-1, ICAM-1 and selectins on endothelial cell surface, and migration of leukocytes and monocytes/macrophages to the subendothelial space, which is mediated by oxidized LDL, MCP-1, PDGF and MCSF. This is followed by smooth muscle cell migration from vascular media to the intima and their proliferation (stimulated by PDGF and TGF-β), T-cell activation (stimulated by TNF-α and IL-2), conversion of lipid-laden macrophages to so-called foam cells (stimulated by oxidized LDL, MCSF, TNF-α and IL-1), and platelet accumulation stimulated by the factors such as thromboxane A2, tissue factor, etc. Platelet accumulation is also stimulated by the fact that hyperlipidemia, and hypertriglyceridemia in particular, promote the synthesis of PAI-1 in endothelial cells, and PAI-1 is known to play a major role in atherogenesis by decreasing fibrinolytic activity and stimulating thrombogenesis. Smooth muscle cells form a connective cap over the lipid core of atheroma, thus separating the lipid core from the vascular lumen and the blood. A number of factors, of which the composition of atheroma is of crucial importance, determine whether the atheroma will remain stable or its cap will sustain rupture to form a thromb at the site. Rupture of the atheroma cap occurs primarily due to the activation

proteolitičke enzime koji dovode do razgradnje vezivnog tkiva kape ateroma i njenog pucanja. Pritom dolazi do prodiranja krvi iz lumena žile u aterom ili do krvarenja iz vasa vasorum, a kako su lipidi iz jezgre ateroma i pjenaste stanice izrazito trombogeni, nastaje tromb koji može povećati aterom, ali gdjekada i začepiti arteriju, a potiče se i vazospazam. Trombogenezi doprinosi i tzv. tkivni čimbenik iz stanica ateroma. S druge pak strane tromboza potiče upalni proces nastavljajući opisana zbivanja, jer potiče izraženost P selektina i liganda CD40 na površini trombocita, a te molekule potiču novačenje leukocita i upalni proces. Opisana zbivanja uzrokuju nestabilnu anginu pektoris (ako tromb ne začepi potpuno lumen koronarne arterije) i akutni infarkt miokarda (ako dođe do potpune okluzije arterije), odnosno tzv. non-Q infarkt miokarda (ako se radi o potpunoj, ali privremenoj i prolaznoj okluziji). Takvi se ateromi nazivaju nestabilnim ili vulnerabilnim. Apoptotička smrt stanica kao što su makrofazi i glatke mišićne stanice također potiče nestabilnost ateroma. Nestabilni ateromi sadrže mnogo lipida, brojne upalne stanice i imaju tanku vezivnu kapu koja sadrži malo veziva. Za razliku od njih, stabilni ateromi imaju debelu vezivnu kapu, malu lipidnu jezgru i malo upalnih stanica. Premda se smatra da samo mali broj ateroma u koronarnim arterijama koji se uoče tehnikama vizualnog prikaza spada u one nestabilne, upravo su oni odgovorni za većinu pogibeljnih koronarnih zbivanja.

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of macrophages (influenced by inflammatory cells, T lymphocytes in particular) that secrete metalloproteinases (collagenases, elastases) and other proteolytic enzymes, which in turn lead to degradation of the atheroma connective cap and its rupture. This results in blood migration from vascular lumen into the atheroma or in hemorrhage from vasa vasorum; as the lipids from the atheroma core and foam cells are extremely thrombogenic, a thromb is formed which may enlarge the atheroma, or occasionally occlude the artery, also stimulating vasospasm. The so-called tissue factor from the cells of the atheroma also contributes to thrombogenesis. On the other hand, thrombosis stimulates inflammatory process by perpetuating these events because it stimulates the expression of P selectin and CD40 ligand on platelet surface, and these molecules stimulate leukocyte recruitment and inflammatory process. All these events cause unstable angina pectoris (in case of incomplete coronary artery lumen occlusion by thrombus) or acute myocardial infarction (complete arterial occlusion) or so-called non-Q myocardial infarction (complete but temporary and transient occlusion). This type is known as unstable or vulnerable atheroma. Atheroma instability is also favored by apoptotic death of cells such as macrophages and smooth muscle cells. Unstable atheroma contains an abundance of lipids and inflammatory cells, and has a thin connective cap containing some connective tissue. In contrast, stable atheroma has a thick connective cap, small lipid nucleus, and some inflammatory cells. Although only a small proportion of coronary artery atheromas visualized by imaging techniques are considered to belong to the unstable form, they are responsible for the majority of fatal coronay events.

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PL2

Pedijatrijska laboratorijska medicina: zašto je drukčija?

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PL2

Pediatric laboratory medicine: why is it different?

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Veći dio svog radnog vijeka provela sam u dječjoj bolnici, gdje sam se neposredno uvjerila kako "djeca nisu tek male odrasle osobe", nego predstavljaju raspon od nedonoščadi do druge novorođenčadi, dojenčadi, djece u razvoju, mladeži i mladih odraslih osoba. Pred pedijatri-

Much of my career has been spent in a children's hospital, where I became acutely aware that „children are not just small adults". They range from premature babies to other neonates, infants, developing children, adolescents, and young adults. There are many challenges for the pediatric

jskim laboratorijem stoje mnogi izazovi, od potrebe za primjenom malih uzoraka, promjene referentnih intervala s dobi, potrebe za brzim pretragama do izazova što ih postavljaju adolescenti te mogućnosti izvođenja pretraga za genetičke i metaboličnе bolesti. Raspravljati će se o odgovorima na ove izazove, a oni obuhvaćaju ispravno prikupljanje novorođenačkih uzoraka, pitanja vezana uz mali volumen krvi kod novorođenčadi, dobnu raznovrsnost u pedijatriji, zbog čega adolesenti predstavljaju izazov u današnjem okruženju, testiranje uz bolesnika, te kako pristupiti testiranju za metaboličnе bolesti.

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laboratory, from the need to use small samples, changing reference intervals with age, the necessity for rapid testing, the challenges of adolescents, and the ability to test for genetic and metabolic diseases. The answers to these challenges will be discussed. They include proper collection of neonatal specimens, issues of the small blood volume of neonates, the age diversity in pediatrics, why adolesents are challenging in today's environment, Point-of-Care testing, and how to approach testing for metabolic diseases.

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PL3

Farmakogenetika, farmakogenomika i farmakoproteomika kardiovaskularnih lijekova

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Kad statin ili diuretik dajemo skupini bolesnika, neki od njih odgovaraju sniženjem kolesterola ili krvnog tlaka, a drugi pak ne. U ove različite odgovore uključeno je pet skupina gena:

- Prvu skupinu čine geni koji reguliraju farmakokinetsko ponašanje dotičnog lijeka. Najčešće su tu upleteni citokrom P450 2D6 i C9-C19. Međutim, trebamo slijediti ulogu prijenosnika, poglavito porodica ABC.
- Druga važna skupina su farmakološki ciljni geni uz receptore i enzime koji imaju glavnu ulogu u genetskoj raznolikosti koja se očituje kod statina ili antihipertenzivnih lijekova.
- Ipak, ne smijemo zaboraviti gene uključene u patologije koje mijenjaju metaboličke cikluse, fiziološke i čimbenike okoliša u regulaciji ekspresije ovih gena. Razvoj područja farmakogenomike kroz koncept biologije sustava treba isto tako obuhvatiti i proteome .
- Mnogi proteini ili peptidi izravno su odgovorni za raznolikost odgovora na terapijsku intervenciju. Polimorfizam apoE mogao bi biti dobrim modelom za objašnjavanje – kroz različite biofizikalne strukture izoforma (farmakogenomika i farmakoproteomika)

PL3

Pharmacogenetics, pharmacogenomics and pharmacoproteomics of cardiovascular drugs

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When we are giving a statin or diuretic drug to a group of patients, some are responding by a decrease in cholesterol or blood pressure but others do not. Five groups of genes are involved in these different responses :

- The first one are the genes regulating the pharmacokinetic behaviour of the drug. Cytochrome P450 2D6 and C9-C19 are the most frequently involved. But we have to follow the role of the transporters, particularly the ABC families.
- The pharmacological targets genes are the second important group with the receptors and the enzymes which play the major role in the genetic variability found with statins or antihypertensive drugs.
- Yet we should not forget the genes implicated in the pathologies modifying the metabolic cycles, the physiological and environmental factors in the regulation of the expression of these genes. The evolution of the field of pharmacogenomics through the concept of system biology should also include the proteomes.
- Many proteins or peptides are directly responsible for the variability in the response to therapeutic intervention. ApoE polymorphism could be a good

– različitih učinaka mnogih lijekova ili prehrambenih sastojaka.

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model explaining – through different biophysical structure of the isoforms (pharmacogenomics and pharmacoproteomics) – the different effects of many drugs or dietary compounds.

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PL4

Medicinska biokemija i laboratorijska medicina: pogled u budućnost

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Posljednja desetljeća obilježena su značajnim promjenama u pobolu i smrtnosti u čitavom svijetu: ekonomski razvijene zemlje su sve više pod pritiskom epidemija zaraznih bolesti poput SARS, ptičje gripe, drugih virusnih bolesti, infekcija rezistentnim sojevima bakterija ili TBC, te AIDS/HIV, a zemlje u razvoju ili nerazvijene uz postojeće zarazne bolesti pokazuju veći pobol od kroničnih nezaraznih bolesti, među kojima prevladava dijabetes. Ekonomski razvoj zemlje je nepobitno povezan sa zdravljem ljudi pa je investicija u zdravlje ujedno investicija u ekonomski razvoj isto koliko i poboljšanje pokazatelja zdravstvenog stanja stanovništva. U ciljevima milenijskog programa Svjetske zdravstvene organizacije težište se stavlja na pravo na zdravlje osobito vulnerabilnih skupina pa se od zemalja članica očekuje da takav program provedu u svojoj nadležnosti. Kako se globalne promjene u pobolijevanju i širenju bolesti mogu odraziti na laboratorijsku medicinu s organizacijskog, stručnog i znanstvenog pogleda te razvoja discipline u budućnosti? Znanstvena dostignuća u području tehnologijskog razvoja dijagnostičkih disciplina omogućuju budućnost laboratorijskoj medicini, osobito u području rješavanja javnozdravstvenih problema te u novoj disciplini javnog zdravstva nazvanoj pokret za promicanje zdravlja. Nove tehnologije potaknute minijaturizacijom strojeva, povećanjem radnog kapaciteta dijagnostičkih instrumenata i napretkom u primjeni genomike u dijagnostici značajno povećavaju ulogu dijagnostičkih disciplina u zdravstvenom sustavu. One omogućavaju dosad neviđenu brzinu postupka, sve više dijagnostičkih postupaka uz bolesnika, dok novi biomarkeri vode ka jednom od ciljeva suvremene medicine, tzv. personaliziranoj zdravstvenoj skrbi. Nove mogućnosti razvoja biomarkera za infektivne bolesti, genetički uvjetovane bolesti, molekularnu onkologiju, farmakogenomiku

PL4

Medical biochemistry and laboratory medicine: future prospects

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The last decades have been characterized by considerable changes in the morbidity and mortality rates worldwide; industrialized countries are increasingly burdened with the epidemics of infectious diseases such as SARS, avian influenza, other viral diseases, infection with resistant bacterial strains or tuberculosis, and AIDS/HIV, whereas developing and less industrialized countries show an ever greater morbidity of chronic noncommunicable diseases, primarily diabetes, in addition to the existing infectious diseases. The economic development of a country is closely related to human health, thus investment in health means investment in economy and improvement in the indicators of the population health state. The goals posed by the millennium program of the World Health Organization are focused on the right to health with special reference to the vulnerable population groups. Member countries are expected to implement the program by their authorities. What might be the impact of global changes in the prevalence and spread of diseases on laboratory medicine from the structural, professional and scientific aspects, and on the overall discipline development in the future? Scientific achievements in the field of technological development of diagnostic disciplines ensure the future of laboratory medicine, especially in the solving public health problems as well as in the new public health discipline referred to as the movement of health promotion. New technologies incited by miniaturization of devices, extended performance of diagnostic instruments and advancement in the diagnostic use of genomics have significantly increased the role of diagnostic disciplines in the health care system. They have enabled an unprecedented rapidity of procedures and an increasing proportion of point-of-care testing, whereas novel biomarkers lead to one of the

te prediktivnu medicinu stavljaju *in vitro* dijagnostiku u središnji dio zdravstvenog sustava. Razvoj biomarkera za personaliziranu medicinu dovodi dijagnostičku industriju bliže farmaceutskoj, jer je osnovni cilj jedne i druge pratiti odgovarajućim novim biomarkerima izbor odgovarajućeg lijeka, odgovor na njegovu primjenu u postizanju dobrog ishoda za pojedinog bolesnika. Zato se ubuduće očekuje promjena odnosa između stručnjaka laboratorijske medicine, proizvođača dijagnostičkih testova i proizvođača lijekova. Novi biomarkeri će usmjeravati razvoj lijekova, klinička istraživanja, praćenje i evaluaciju ishoda te doprinijeti time afirmaciji medicine zasnovane na dokazima. Primjena laboratorijske medicine zasnovane na dokazima je ekonomski zahtjevna te u cilju snižavanja troškova u zdravstvu postoji jasna tendencija proizvođača dijagnostičkih proizvoda da harmoniziraju svoje proizvode, što omogućava nižu cijenu uz kvalitetniju primjenu u svim dijelovima svijeta. Globalizacija tržišta vodi pak ka promjeni organizacije laboratorijske dijagnostike u dva smjera: primjene iste uz bolesnika odnosno konsolidaciji velikih laboratorija s obzirom na tehnologije, a ne isključivo specijalnosti i subspecijalnosti struka. Zahtjevni novi tehnološki procesi, globalizacija znanja, brza izmjena novih spoznaja zahtijevaju promjene u izobrazbi stručnjaka-specijalista laboratorijske medicine. Cjeloživotno učenje, primjena e-edukacije (*e-learning*), dobivanje i produžavanje ovlaštenja za određene specifične dijagnostičke postupke su zahtjevi bez kojih se ne mogu kompetentno obavljati profesionalne obveze. I konačno laboratorijski stručnjaci ubuduće će sve više biti promicatelji svojih profesionalnih vještina u komunikaciji s bolesnicima ili sveukupnom javnošću, što im postavlja zadaću svladavanja novih komunikacijskih vještina.

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major goals of current medicine, i.e. personalized health care. The new developments in the field of biomarkers for infectious diseases, genetic diseases, molecular oncology, pharmacogenomics and predictive medicine put the *in vitro* diagnosis in the very center of the health care system. The development of biomarkers for personalized medicine brings diagnostic industry closer to pharmaceutical industry because both of them primarily tend to follow proper drug choice and therapeutic response leading to favorable outcome in a particular patient by use of appropriate new biomarkers. Thus, the relationships between laboratory medicine professionals, diagnostic test manufacturers and drug manufacturers are expected to undergo modifications in the future. The new biomarkers will direct the development of drugs, clinical trials, follow up and outcome evaluation, and will contribute to the recognition of evidence based medicine. The use of evidence based laboratory medicine is economically demanding, therefore there is clear trend among diagnostic product manufacturers to harmonize their products, thus allowing for cost reduction along with their high quality utilization all over the world, all this in order to reduce the cost of health care in general. Market globalization, in turn, will entail dual changes in the structure of laboratory diagnosis, i.e. use of point-of-care testing and consolidation of large laboratories in terms of technology rather than exclusively specialties and subspecialties. The novel demanding technological processes, globalization of knowledge, and fast exchange of new concepts require modifications in the education of laboratory medicine professionals. Life-long learning, use of e-learning, licensing and relicensing for particular specific diagnostic procedures are the requirements without which professional commitments cannot be competently performed. And the last but not the least, in the future, laboratory professionals will increasingly take the role of their professional skill promotors in their contact with patietns or the public in general, imposing the need of mastering some new communication skills.

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