doi: 10.3325/cmj.2009.51.96

CROATIAN INTERNATIONAL PUBLICATIONS

by Ivan Krešimir Lukić

iklukic@mef.hr

Lauc G, Rudan I, Campbell H, Rudd PM. Complex genetic regulation of protein glycosylation. Mol Biosyst. 2010;6:329-35

University of Zagreb, Faculty of Pharmacy and Biochemistry, Zagreb

One hundred years have passed since Archibald Garrod postulated the one gene/one enzyme hypothesis. Since then, science has made significant progress and geneticists are now tackling an overwhelming complexity of gene regulation networks that underlie the genetics of complex human diseases. A particularly complex element in the biology of higher organisms is the genetics of protein glycosylation. Nearly all proteins that appeared after the emergence of multicellular life are glycosylated, but instead of being molded by a single gene, glycan structures are encoded within a network of several hundred glycosyltransferases, glycosidases, transporters, transcription factors and other proteins. In addition, in contrast to the linear structures of DNA and proteins, glycans have multiple branches that make their analysis significantly more challenging. However, recent developments in high throughput HPLC analysis have advanced glycan analysis significantly and it is now possible to address questions about the complex genetics of protein glycosylation. In this review we present some preliminary insights into this fascinating field.

Igl W, Johansson A, Wilson JF, Wild SH, Polašek O*, Hayward C et al. Modeling of environmental effects in genome-wide association studies identifies SLC2A2 and HP as novel loci influencing serum cholesterol levels. PLoS Genet. 2010;6:e1000798

**Andrija Štampar School of Public Health, Faculty of Medicine, University of Zagreb, Zagreb*

Genome-wide association studies (GWAS) have identified 38 larger genetic regions affecting classical blood lipid levels without adjusting for important environmental influences. We modeled diet and physical activity in a GWAS in order to identify novel loci affecting total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride levels. The Swedish (SE) EUROSPAN cohort (N(SE) = 656) was screened for candidate genes and the non-Swedish (NS) EUROSPAN cohorts (N(NS) = 3,282) were used for replication. In total, 3 SNPs were associated in the Swedish sample and were replicated in the non-Swedish cohorts. While SNP rs1532624 was a replication of the previously published association between CETP and HDL cholesterol, the other two were novel findings. For the latter SNPs, the p-value for association was substantially improved by inclusion of environmental covariates: SNP rs5400 (p(SE,unadjusted) = 3.6 x 10(-5), p(SE,adjusted) = 2.2 x 10(-6), p(NS,unadjusted) = 0.047) in the SLC2A2 (Glucose transporter type 2) and rs2000999 (p(SE,unadjusted) = 1.1 x 10(-3), p(SE,adjusted) = 3.8 x 10(-4), p(NS,unadjusted) = 0.035) in the HP gene (Haptoglobin-related protein precursor). Both showed evidence of association with total cholesterol. These results demonstrate that inclusion of important environmental factors in the analysis model can reveal new genetic susceptibility loci.

Sambunjak D, Straus SE, Marušić A. A systematic review of qualitative research on the meaning and characteristics of mentoring in academic medicine. J Gen Intern Med. 2010;25:72-8

Croatian Medical Journal, Zagreb, Croatia.

BACKGROUND: Mentorship is perceived to play a significant role in the career development and productivity of academic clinicians, but little is known about the characteristics of mentorship. This knowledge would be useful for those developing mentorship programs. OBJECTIVE: To complete a systematic review of the qualitative literature to explore and summarize the development, perceptions and experiences of the mentoring relationship in academic medicine. DATE SOURCES: Medline, PsycINFO, ERIC, Scopus and Current Contents databases from the earliest available date to December 2008. REVIEW METHODS: We

included studies that used qualitative research methodology to explore the meaning and characteristics of mentoring in academic medicine. Two investigators independently assessed articles for relevance and study quality, and extracted data using standardized forms. No restrictions were placed on the language of articles. RESULTS: A total of 8,487 citations were identified, 114 full text articles were assessed, and 9 articles were selected for review. All studies were conducted in North America, and most focused on the initiation and cultivation phases of the mentoring relationship. Mentoring was described as a complex relationship based on mutual interests, both professional and personal. Mentees should take an active role in the formation and development of mentoring relationships. Good mentors should be sincere in their dealings with mentees, be able to listen actively and understand mentees' needs, and have a well-established position within the academic community. Some of the mentoring functions aim at the mentees' academic growth and others at personal growth. Barriers to mentoring and dysfunctional mentoring can be related to personal factors, relational difficulties and structural/institutional barriers. CONCLUSIONS: Successful mentoring requires commitment and interpersonal skills of the mentor and mentee, but also a facilitating environment at academic medicine's institutions.

Novak I, Kirkin V, McEwan DG, Zhang J, Wild P, Rozenknop A et al. Nix is a selective autophagy receptor for mitochondrial clearance. EMBO Rep. 2010;11:45-51

Mediterranean Institute for Life Sciences, Split, Croatia

Autophagy is the cellular homeostatic pathway that delivers large cytosolic materials for degradation in the lysosome. Recent evidence indicates that autophagy mediates selective removal of protein aggregates, organelles and microbes in cells. Yet, the specificity in targeting a particular substrate to the autophagy pathway remains poorly understood. Here, we show that the mitochondrial protein Nix is a selective autophagy receptor by binding to LC3/GABARAP proteins, ubiquitin-like modifiers that are required for the growth of autophagosomal membranes. In cultured cells, Nix recruits GABARAP-L1 to damaged mitochondria through its amino-terminal LC3-interacting region. Furthermore, ablation of the Nix:LC3/GABARAP interaction retards mitochondrial clearance in maturing murine reticulocytes. Thus, Nix functions as an autophagy receptor, which mediates mitochondrial clearance after mitochondrial damage and during erythrocyte differentiation.

Dujić Ž, Uglešić L, Brešković T, Valić Z, Heusser K, Marinović J, Ljubković M, Palada I. Involuntary breathing movements improve cerebral oxygenation during apnea struggle phase in elite divers. J Appl Physiol. 2009;107:1840-6

Department of Physiology, University of Split School of Medicine, Split, Croatia

We investigated whether the involuntary breathing movements (IBM) during the struggle phase of breath holding, together with peripheral vasoconstriction and progressive hypercapnia, have a positive effect in maintaining cerebral blood volume. The central hemodynamics, arterial oxygen saturation, brain regional oxyhemoglobin (bHbO(2)), deoxyhemoglobin, and total hemoglobin changes and IBM were monitored during maximal dry breath holds in eight elite divers. The frequency of IBM increased (by approximately 100%), and their duration decreased (approximately 30%), toward the end of the struggle phase, whereas the amplitude was unchanged (compared with the beginning of the struggle phase). In all subjects, a consistent increase in brain regional deoxyhemoglobin and total hemoglobin was also found during struggle phase, whereas bHbO(2) changed biphasically: it initially increased until the middle of the struggle phase, with the subsequent relative decline at the end of the breath hold. Mean arterial pressure was elevated during the struggle phase, although there was no further rise in the peripheral resistance, suggesting unchanged peripheral vasoconstriction and implying the beneficial influence of the IBM on the cardiac output recovery (primarily by restoration of the stroke volume). The IBM-induced short-lasting, sudden increases in mean arterial pressure were followed by similar oscillations in bHbO(2). These results suggest that an increase in the cerebral blood volume observed during the struggle phase of dry apnea is most likely caused by the IBM at the time of the hypercapnia-induced cerebral vasodilatation and peripheral vasoconstriction.

Guić MM, Kosta V, Aljinović J, Sapunar D, Grković I. Characterization of spinal afferent neurons projecting to different chambers of the rat heart. Neurosci Lett. 2010 29;469:314-8

Department of Anatomy, Histology and Embriology, Split School of Medicine, Split, Croatia

The pattern of distribution of spinal afferent neurons (among dorsal root ganglia-DRGs) that project to anatomically and functionally different chambers of the

rat heart, as well as their morphological and neurochemical characteristics were investigated. Retrograde tracing using a patch loaded with Fast blue (FB) was applied to all four chambers of the rat heart and labeled cardiac spinal afferents were characterized by using three neurochemical markers. The majority of cardiac projecting neurons were found from T1 to T4 DRGs, whereas the peak was at T2 DRG. There was no difference in the total number of FB-labeled neurons located in ipsilateral and contralateral DRGs regardless of the chambers marked with the patch. However, significantly more FB-labeled neurons projected to the ventricles compared to the atria (859 vs. 715). The proportion of isolectin B(4) binding in FB-labeled neurons was equal among all neurons projecting to different heart chambers (2.4%). Neurofilament 200 positivity was found in greater proportions in DRG neurons projecting to the left side of the heart, whereas calretinin-immunoreactivity was mostly represented in neurons projecting to the left atrium. Spinal afferent neurons projecting to different chambers of the rat heart exhibit a variety of neurochemical phenotypes depending on binding capacity for isolectin B(4) and immunoreactivity for neurofilament 200 and calretinin, and thus represent important baseline data for future studies.

Kojundžić SL, Puljak L, Hogan Q, Sapunar D. Depression of Ca(2+)/calmodulin-dependent protein kinase II in dorsal root ganglion neurons after spinal nerve ligation. J Comp Neurol. 2010;518:64-74

Department of Anatomy, Histology and Embryology, University of Split School of Medicine, Split, Croatia.

The enzyme calcium/calmodulin-dependent protein kinase II (CaMKII) is associated with memory and its alpha isoform is critical for development of activity-induced synaptic changes. Therefore, we hypothesized that CaMKII is involved in altered function of dorsal root ganglion (DRG) neurons after neuronal injury. To test this hypothesis, Sprague-Dawley rats were made hyperalgesic by L5 and L6 spinal nerve ligation (SNL), and changes in total phosphorylated and unphosphorylated CaMKII (tCaMKII) and phosphorylated form of its alpha isoform (pCaMKIIalpha) were analyzed using immunochemistry in different subpopulations of DRG. SNL did not induce any changes in tCaMKII between experimental groups, while the overall percentage of pCaMKIIalpha-positive neurons in injured L5 DRG SNL (24.8%) decreased significantly when compared to control (41.7%). SNL did not change the percentage of pCaMKIIalpha/N52 colabeled neurons but decreased the percentage of N52-negative nonmyelinated neurons that expressed pCaMKIIalpha from 27% in control animals to 11% after axotomy. We also observed a significant decrease in the percentage of small nonpeptidergic neurons labeled with IB4 (37.6% in control vs. 4.0% in L5 SNL DRG), as well as a decrease in the percentage of pCaMKIIalpha/IB4 colabeled neurons in injured L5 DRGs (27% in control vs. 1% in L5 DRG of SNL group). Our results show that reduction in pCaMKIIalpha levels following peripheral injury is due to the loss of IB4-positive neurons. These results indicate that diminished afferent activity after axotomy may lead to decreased phosphorylation of CaMKIIalpha.