CROATIAN INTERNATIONAL PUBLICATIONS

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Mudnić I, Budimir D, Jajić I, Boban N, Sutlović D, Jerončić A, Boban M. Thermally treated wine retains vasodilatory activity in rat and guinea pig aorta. J Cardiovasc Pharmacol. 2011;57:707-11.

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In contrast to the intact wine, cardiovascular effects of the thermally treated wine have not been studied, despite widespread habits of cooking with wine and consumption of mulled wine. Vasodilatory effects of the red wine heated at 75 and 125°C were examined in the isolated rat and guinea pig aorta and compared with the intact and wine dealcoholized without thermal stress. Samples were analyzed for their phenolic content, antioxidant capacity, resveratrol and ethanol contents. Heating-induced degradation of individual phenolic fraction was observed only in the samples treated at 125°C, although total phenolic concentration and related antioxidant activity increased in the thermally treated samples due to the reduction in their volume. All wine samples regardless of treatment caused similar maximal relaxation in both species, but the response was stronger in aortas from guinea pigs. At the lowest concentrations up to 1‰, dealcoholized wine produced vasodilation greater than that produced by intact wine and wines treated at 75 and 125°C, which showed similar vasodilating activity at all concentrations. Our results indicate that wine thermally treated under heating conditions applicable to the preparation of a mulled wine and cooking with wine largely retains vasodilatory activity in vitro despite significant heat-induced changes in its composition.

Pyzik M, Charbonneau B, Gendron-Pontbriand EM, Babić M*, Krmpotić A*, Jonjić S*, Vidal SM. Distinct MHC class I-dependent NK cell-activating receptors control cytomegalovirus infection in different mouse strains. J Exp Med. 2011;208:1105-17.

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Recognition of mouse cytomegalovirus (MCMV)-infected cells by activating NK cell receptors was first described in the context of Ly49H, which confers resistance to C57BL/6 mice. We investigated the ability of other activating Ly49 receptors to recognize MCMV-infected cells in mice from various H-2 backgrounds. We observed that Ly49P1 from NOD/Ltj mice, Ly49L from BALB mice, and Ly49D2 from PWK/Pas mice respond to MCMV-infected cells in the context of H-2D(k) and the viral protein m04/gp34. Recognition was also seen in the H-2(d) and/or H-2(f) contexts, depending on the Ly49 receptor examined, but never in H-2(b). Furthermore, BALB.K (H-2(k)) mice showed reduced viral loads compared with their H-2(d) or H-2(b) congenic partners, a reduction which was dependent on interferon γ secretion by Ly49L(+) NK cells early after infection. Adoptive transfer of Ly49L(+), but not Ly49L(-), NK cells significantly increased resistance against MCMV infection in neonate BALB.K mice. These results suggest that multiple activating Ly49 receptors participate in H-2-dependent recognition of MCMV infection, providing a common mechanism of NK cell-mediated resistance against viral infection.

Polašek O, Leutenegger AL, Gornik O, Zgaga L, Kolčić I, McQuillan R, Wilson JF, Hayward C, Wright AF, Lauc G, Campbell H, Rudan I. Does inbreeding affect N-glycosylation of human plasma proteins? Mol Genet Genomics. 2011;285:427-32.

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Inbreeding depression and heterosis are the two ends of phenotypic changes defined by the genome-wide homozygosity. The aim of this study was to investigate the association of genetic marker-based homozygosity estimates with 46 N-glycan features measured in human plas-

ma. The study was based on a total of 2,341 subjects, originating from three isolated island communities in Croatia (Vis and Korcula islands) and Scotland (Orkney Islands). Inbreeding estimates were associated with an increase in tetrantennary and tetrasialylated glycans, and a decrease in digalactosylated glycans ($P < 0.001$). The strength of this association was proportional to the mean cohort-based inbreeding coefficient. Increase in tetraantennary glycans is known to be associated with various tumours and their association with inbreeding might be one of the mechanisms underlying the increased prevalence of tumours reported in some human isolated populations. Further studies are thus merited in order to confirm the association of inbreeding with changes in glycan profiles in other plant and animal populations, thus attempting to establish if glycosylation could indeed be involved in mediation of some phenotypic changes described in inbred and outbred organisms.

Puljak L, Sapunar D. Web-based elective courses for medical students: an example in pain. Pain Med. 2011;12:854-63.

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Objective. Online learning is an efficient new educational method that is able to link teachers with geographically dispersed students and capture the interest of students with interactive materials. Our objective was to describe curricula of new Web-based electives about pain for undergraduate medical education. Design. We created three interactive Web-based elective courses about pain targeted to medical and dental students. "The Puzzle of Pain" course introduced basic concepts of pain and neurobiology of pain. The humanities-based curriculum of "Empathy and Pain" taught students about emotional aspects of pain and empathetic responses. "The Cochrane Library and Pain" course introduced students to the concept of evidence-based medicine, critical appraisal of the literature, and the hierarchy of evidence in medicine. Outcome Measures. We measured program effectiveness with a pretest/posttest instrument and student satisfaction survey. Results. Mean knowledge scores increased significantly after the program and overall evaluations were positive. Conclusions. Delivering the pain electives for medical students in an online format was an efficient educational method, with high student satisfaction scores. Medical educators should consider online electives for medical students in pain studies as well as in other content areas.

Sedić M, Kraljević Pavelić S, Cindrić M, Vissers JP, Peronja M, Josić D, Ćuk M, Fumić K, Pavelić K, Barić I. Plasma biomarker identification in S-adenosylhomocysteine hydrolase deficiency.Electrophoresis. 2011;32:1970-5.

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S-Adenosylhomocysteine hydrolase (AHCY) deficiency is a rare congenital disorder in methionine metabolism clinically characterized by white matter atrophy, delayed myelination, slowly progressive myopathy, retarded psychomotor development and mildly active chronic hepatitis. In the present study, we utilized a comparative proteomics strategy based on 2-DE/MALDI-MS and LC/ESI-MS to analyze plasma proteins from three AHCY-deficient patients prior to and after receiving dietary treatment designed to alleviate disease symptoms. Obtained results revealed candidate biomarkers for the detection of myopathy specifically associated with AHCY deficiency, such as carbonic anhydrase 3, creatine kinase, and thrombospondin 4. Several proteins mediating T-cell activation and function were identified as well, including attractin and diacylglycerol kinase α. Further validation and functional analysis of identified proteins with clinical value would ensure that these biomarkers make their way into routine diagnosis and management of AHCY deficiency.

Chi J, Ballabio E, Chen XH, Kušec R*, Taylor S, Hay D, Tramonti D, Saunders NJ, Littlewood T, Pezzella F, Boultwood J, Wainscoat JS, Hatton CS, Lawrie CH. MicroRNA expression in multiple myeloma is associated with genetic subtype, isotype and survival. Biol Direct. 2011;6:23.

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BACKGROUND: MicroRNAs are small RNA species that regulate gene expression post-transcriptionally and are aberrantly expressed in many cancers including hematological malignancies. However, the role of microRNAs in the pathogenesis of multiple myeloma (MM) is only poorly understood. We therefore used microarray analysis to elucidate the complete miRNome (miRBase version 13.0) of purified tumor (CD138+) cells from 33 patients with MM, 5 patients with monoclonal gammopathy of undetermined significance (MGUS) and 9 controls.

RESULTS: Unsupervised cluster analysis revealed that MM and MGUS samples have a distinct microRNA

expression profile from control CD138+ cells. The majority of microRNAs aberrantly expressed in MM (109/129) were up-regulated. A comparison of these microRNAs with those aberrantly expressed in other B-cell and T-cell malignancies revealed a surprising degree of similarity (~40%) suggesting the existence of a common lymphoma microRNA signature. We identified 39 microRNAs associated with the pre-malignant condition MGUS. Twenty-three (59%) of these were also aberrantly expressed in MM suggesting common microRNA expression events in MM progression. MM is characterized by multiple chromosomal abnormalities of varying prognostic significance. We identified specific microRNA signatures associated with the most common IgH translocations (t(4;14) and t(11;14)) and del(13q). Expression levels of these microRNAs were distinct between the genetic subtypes (by cluster analysis) and correctly predicted these abnormalities in > 85% of cases using the support vector machine algorithm. Additionally, we identified microRNAs associated with light chain only myeloma, as well as IgG and IgA-type MM. Finally, we identified 32 microRNAs associated with event-free survival (EFS) in MM, ten of which were significant by univariate (logrank) survival analysis.

CONCLUSIONS: In summary, this work has identified aberrantly expressed microRNAs associated with the diagnosis, pathogenesis and prognosis of MM, data which will prove an invaluable resource for understanding the role of microRNAs in this devastating disease.

Šantić M, Ozanić M, Semić V, Pavoković G, Mrvčić V, Kwaik YA. Intra-vacuolar Proliferation of F. novicida within H. vermiformis. Front Microbiol. 2011;2:78.

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Francisella tularensis is a gram negative facultative intracellular bacterium that causes the zoonotic disease tularemia. Free-living amebae, such as Acanthamoeba and Hartmannella, are environmental hosts of several intracellular pathogens. Epidemiology of F. tularensis in various parts of the world is associated with water-borne transmission, which includes mosquitoes and amebae as the potential host reservoirs of the bacteria in water resources. In vitro studies showed intracellular replication of F. tularensis within A. castellanii cells. Whether ameba is a biological reservoir for Francisella in the environment is not known. We used Hartmannella vermiformis as an amebal model system to study the intracellular life of F. novicida. For the first time we show that F. novicida survives and replicates within H. vermiformis. The iglC mutant strain of F. novicida is defective for survival and replication not only within A. castellanii but also in H. vermiformis cells. In contrast to mammalian cells, where bacteria replicate in the cytosol, F. novicida resides and replicates within membrane-bound vacuoles within the trophozoites of H. vermiformis. In contrast to the transient residence of F. novicida within acidic vacuoles prior to escaping to the cytosol of mammalian cells, F. novicida does not reside transiently or permanently in an acidic compartment within H. vermiformis when examined 30 min after initiation of the infection. We conclude that F. tularensis does not replicate within acidified vacuoles and does not escape into the cytosol of H. vermiformis. The Francisella pathogenicity island locus iglC is essential for intra-vacuolar proliferation of F. novicida within H. vermiformis. Our data show a distinct intracellular lifestyle for F. novicida within H. vermiformis compared to mammalian cells.