These research projects were undertaken in partial fulfillment of the requirements for the MD degree at Sackler Faculty of Medicine, Tel Aviv University in 2015–2016, They were considered the most outstanding of the graduating class

Kinetic and equilibrium properties of regulatory Ca2+–binding domains in sodium–calcium exchangers 2 and 3

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Lessons to learn

- Alternative splicing of NCX3 mainly affects Ca2+-binding dynamics, not Ca2+ affinity.
- A-exon containing NCX3 is mainly expressed in skeletal muscle (slow Ca2+ transients), whereas B-exon containing NCX3 is mainly expressed in the brain (fast Ca2+ transients).
- CBD1 interacts with CBD2 in the context of the CBD12 tandem in NCX isoforms, where these interactions specifically modulate Ca2+ sensing at the primary sensor of CBD1 to meet the physiological requirements

Correlation between 'ACKR1/DARC null' polymorphism and benign neutropenia in Yemenite Jews

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Lessons to Learn

- Healthy individuals from various dark skinned populations, including Yemenite Jews, exhibit a unique phenomenon of benign neutropenia, the most common form of neutropenia worldwide. In the present study, we demonstrate the strong and statistically significant correlation between homozygosity of specific single nucleotide polymorphism (SNP) (*rs2814778*) located on chromosome *1q23.2* and the clinical manifestation of benign neutropenia in Yemenite Jews.
- This SNP is located in the promoter region of the *Duffy Antigen Receptor for Chemokines* gene. The homozygous state C/C, designated *DARC*-null allele (*FY-*), results in lack of Duffy antigen expression due to the disruption of the GATA1 erythroid transcription factor binding site. While benign neutropenia and the *FY-* allele do not appear to predispose to regular bacterial infections, it has been found to have an increased susceptibility to HIV infection and on the other hand, a protective effect against malaria.
- Admixture mapping analysis can serve as a predictor of WBC and neutrophil counts in African Americans and Yemenite Jews and also may aid in the differential diagnosis of neutropenia in those patients. Therefore, the results of this study have several clinical implications that can be exploited to improve healthcare.

Laboratory and clinical assessment of a novice technology aimed for continuous monitoring and early identification of hypovolemic shock

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Background: Hemorrhagic shock with occult hypoperfusion is a key challenge to pre-hospital staff during triage and transfer of patients, especially during mass casualty incidents. Recent advances in dynamic light scattering (DLS), and miniaturization of this technology, has resulted in non-invasive sensors capable of continuously monitoring tissue perfusion.
Objectives: To evaluate the ability of miniature DLS (mDLS) sensors to assess hemodynamic status in a porcine model of hemorrhage.
Methods: Following ethics committee approval, anesthetized and ventilated pigs underwent graded hemorrhage and then re-transfusion. Standard vital signs were monitored in conjunction with a thermodilution cardiac output (CO), central venous pressure (CVP), and arterial blood gases. The mDLS sensor was attached to each animal's leg and all monitoring measurements were taken 5 minutes after completion of each period of hemorrhage and re-transfusion to allow equilibration.
Results: All measured parameters changed during bleeding and re-transfusion. During bleeding, *P* values were 0.011 for heart rate (HR), 0.07 for CVP, and ‹ 0.001 for both mean arterial pressure (MAP) and mDLS. During re-transfusion, *P* values were 0.023 for HR, 0.008 for CVP, and ‹ 0.001 for both MAP and mDLS. Pearson's correlation between changes in mDLS and CO demonstrated an *r* value of 0.917 during hemorrhage and 0.965 during re-transfusion. Changes in hemoglobin were not statistically significant during bleeding ($P = 0.331$) but were during re-transfusion ($P = 0.0001$). Changes of bicarbonate, BE, and lactate were found to be statistically significant during both phases of the experiment ($P = 0.001$).
Conclusions: In an animal model of hemorrhagic shock, the mDLS sensor strongly correlates with traditional measures of cardiac output. This initial assessment supports further investigation of this technology in human studies.

Capsule

Interferon-independent antiviral defense

Antiviral responses are normally initiated by interferon production, which stimulates the phosphorylation and activation of STAT1 and STAT2. These transcription factors, together with the transcriptional regulator IRF9, mediate antiviral gene expression. Wang et al. reported that interferon-stimulated gene expression can be mediated by unphosphorylated STAT1 and STAT2 with IRF9 in the absence of interferon production or signaling. This complex protected cells from viral infection and, thus, mediates homeostatic, interferon-independent antiviral responses.

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Eitan Israeli

Capsule

Phthalates and thyroid function in preschool age children: sex-specific associations

Research relating either prenatal or concurrent measures of phthalate exposure to thyroid function in preschool children is inconclusive. In a study of inner-city mothers and their children, metabolites of di-n-butyl phthalate, butylbenzyl phthalate, di-isobutyl phthalate, di(2-ethylhexyl) phthalate, and diethyl phthalate were measured in a spot urine sample collected from women in late pregnancy and from their children at age 3 years. Morgenstern et al. measured children's serum free thyroxine (FT4) and thyroid stimulating hormone (TSH) at age 3. Linear regression models were used to investigate the associations between phthalate metabolites, measured in maternal urine during late pregnancy and measured in child urine at age 3, and thyroid function measured at age 3. Mean concentrations (ranges) were 1.42 ng/dl (1.02–2.24) for FT4, and 2.62 uIU/ml (0.61–11.67) for TSH. In the children at age 3, among girls, FT4 decreased with increasing $\log_e$mono-n-butyl phthalate (estimated b = -0.06; 95% confidence interval [CI] -0.09–0.02), $\log_e$mono-isobutyl phthalate (b = -0.05; 95%CI -0.09–0.01), $\log_e$monoethyl phthalate (b = -0.04; 95%CI -0.07–0.01), and $\log_e$mono(2-ethyl-5-hydroxyhexyl) phthalate (b = -0.04; 95%CI -0.07–0.003) and $\log_e$mono(2-ethyl-5-oxy-hexyl) phthalate (b = -0.04; 95%CI -0.07–0.004). In contrast, among boys the authors observed no associations between FT4 and child phthalate metabolites at age 3. However, in late gestation, FT4 increased with increasing $\log_e$mono-(2-ethylhexyl) phthalate (estimated b = 0.04; 95%CI (0.02–0.06) and no sex difference was observed. They found no associations between phthalate biomarkers measured in either the child or prenatal samples and TSH at age 3.

Environment International 2017; 106: 11

Eitan Israeli

Capsule

Vaccine priming is restricted to draining lymph nodes and controlled by adjuvant-mediated antigen uptake

The innate immune mechanisms by which adjuvants enhance the potency and protection of vaccine-induced adaptive immunity are largely unknown. Liang and co-authors introduced a model to delineate the steps of how adjuvant-driven innate immune activation leads to priming of vaccine responses using rhesus macaques. Fluorescently labeled human immunodeficiency virus (HIV)-1 envelope glycoprotein (Env) was administered together with the conventional aluminum salt (alum) adjuvant. This combination was compared to Env given with alum with preabsorbed Toll-like receptor 7 (TLR7) ligand (alum-TLR7) or the emulsion MF59 because they show superiority over alum for qualitatively and quantitatively improved vaccine responses. All adjuvants induced rapid and robust immune cell infiltration to the injection site in the muscle. This resulted in substantial uptake of Env by neutrophils, monocytes, and myeloid and plasmacytoid dendritic cells (DCs) and migration exclusively to the vaccine-draining lymph nodes. Although less proficient than monocytes and DCs, neutrophils were capable of presenting Env to memory $CD4^+$ T-cells. MF59 and alum-TLR7 showed more pronounced cell activation and overall higher numbers of Env^+ cells compared to alum. This resulted in priming of higher numbers of Env-specific $CD4^+$ T-cells in the vaccine-draining lymph nodes, which directly correlated with increased T-follicular helper cell differentiation and germinal center formation. Thus, strong innate immune activation promoting efficient vaccine antigen delivery to infiltrating antigen-presenting cells in draining lymph nodes is an important mechanism by which superior adjuvants enhance vaccine responses.

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