Precious Molecules

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Fibulin-5 gene causes Age-Related Macular Degeneration (ARMD)

ARMD is the most common cause of irreversible vision loss in the developed world. Stone et al.1 at University of Iowa, USA, carried out an elaborate genetic analysis for mutations in the fibulin gene family in 402 patients of ARMD and 429 control subjects. They screened the DNA, obtained from subjects' blood leukocytes, with a technique called single strand conformational polymorphism (SSCP)2 and confirmed the mutations by sequencing. They identified 7 mutations in the Fibulin-5 gene in 1.7% ARMD patients.

Fibulins are a recently recognized family of extracellular proteins which are widely found in basement membranes (BM) of epithelial cells and blood vessels. They bind other BM proteins such as fibrillin, fibronectin, proteoglycans, elastin and integrins. Fibulin-5 is important for the polymerization of elastin. In 1977 Dr. Donald Gass observed that ARMD patients with a unique kind of drusen - small, round and uniform - were prone to large retinal detachments. This observation suggested that the molecular abnormality which gives rise to this unique type of drusen also altered the attachment of the retinal pigment epithelium to Bruch's membrane. All 7 patients with fibulin-5 mutations in this study, had similar drusen and some degree of retinal pigment epithelium detachment observed on opthalmoscopic examinations.

Elastin is the major component of Bruch's membrane in which drusen form in ARMD. The authors hypothesize that altered expression or activity of fibulin-5 prevents normal elastin polymerization leading to drusen formation and retinal epithelial pigment detachment observed 3 decades ago by Dr. Gass. The authors dedicate this paper in NEJM to Dr. Gass.

1. Stone EM. Missense variations in the fibulin 5 gene and age-related macular degeneration. N Engl J Med. 2004;351:346-53.
2. Sambrook J, Fritsch EF, Maniatis T. Molecular cloning, a laboratory manual, 2nd ed. Cold Spring: Cold Spring Harbour Laboratory Press, New York, 1989.

Molecular basis of Epilepsy

"Neurons that fire together wire together". This is normally the case but in epilepsy this phenomenon is taken to an unhealthy extreme by aberrant wiring of simultaneously firing neurons during a seizure episode through axonal sprouting. This leads to a feed-forward loop facilitating future seizures. Bernard et al.1 report that seizures may be propagated by another mechanism as well. Synaptic signals received at the dendrites not only combine at the soma to generate an action potential, but also generate an echo or a back action potential (b-AP). This echo resonates with the incoming signals in the dendrites and enhances their amplitude. To prevent this AP reverberation from becoming an uncontrolled cycle, a K+ current flows through A-type K+ channels to inhibit it. Bernard et al. showed in a rat model of temporal lobe epilepsy that b-AP was much larger and decreased much less with distance from soma in dendrites of epileptic rats, than normal controls. They investigated the expression and function of A-type K+ channels and found that these channels were decreased in number in dendrites of hippocampal neurons of epileptic rats, while the remaining channels were hyper-activated by phosphorylation through the extracellular signal-regulated kinase (ERK) pathway. Phosphorylation of these channels leads to increased b-AP propagation, by decreasing the voltage required for their activation. This study provides evidence for a new pathway for epilepsy and opens doors for a new class of anti-epileptic drugs.

1. Bernard C. Acquired dendritic channelopathy in

temporal lobe epilepsy. Science. 2004;305:532-5.

Low dose steroids improve survival in septic

Despite antibiotics septic shock has a 30-50% mortality in ICU. The role of high dose steroids in septic shock was investigated in several human clinical trials after bench research suggested the possibility of improved survival, in the 1960s. The results were negative and steroid therapy was contraindicated in septic shock, however, in the 1990s studies showed that septic patients have a relative adrenal insufficiency which may increase mortality.1 This renewed interest in steroid therapy in septic shock but this time at physiological levels. Minneci et al. carried out a meta-analysis comparing studies using high dose steroids versus low dose.2 They found that the low dose steroid trials revealed a consistent beneficial effect of glucocorticoids on survival (OR= 1.23; P=0.04) and shock reversal (OR=1.71; P<0.001). Compared to the high dose trials, the low dose trials administered steroids later (median 23 hours vs <2 hours), for longer durations (6 days vs 1 day) and in lower total dosages (1209 mg vs 23,975 mg hydrocortisone equivalents). Survival was inversely proportional to steroid dose. The authors recommend a 5-7 day regimen of physiologic doses of hydrocortisone (200 -300 mg / day), initiated 24 - 72 hours after vasopressor therapy and followed by a 5-7 day taper to increase survival in septic shock patients.

1. Briegel J. A comparison of the adrenocortical response during septic shock and after complete recovery. Intensive Care Med. 1996 ;22:894-9.
2. Minneci PC. Meta-analysis: the effect of steroids on survival and shock during sepsis depends on the dose. Ann Intern Med. 2004;141:47-56.

Ultrasound screams loud in babies' ears

Mostafa Fatemi and James Greenleaf1, leading ultrasound scientists at Mayo Clinic, Rochester, USA, discovered what they call the "radiation force" of ultrasound (US). In a neat experiment involving 9 volunteer women in late second and third trimesters they evaluated fetal body movements during ultrasonagraphy. They found statistically significant increase in gross fetal movements during exposure to pulsed US Doppler and B modes.2 Radiation force results from an energy change as US beam interacts with an object. Diagnostic US scanners use high intensity narrow beams which exerts a pushing force at the interface of the organ scanned, acting as a needle that repeatedly taps the organ surface. The frequency of this tapping ranges from 1-10kHz, i.e. within the audible frequency range. The pressure this force can generate can be as high as 1700 Pa,
causing significant vibration in the auditory system. This study emphasizes the need for careful interpretation of fetal bio-physical profile tests, fetal body motion studies and fetal hearing tests. Caution needs to be exercised in the frequent use of the obstetric US especially after the fourth month of gestation when the bones of the middle ear ossify, becoming highly reflective and thus likely to receive a stronger radiation force.

http://mayoresearch.mayo.edu/mayo/research/Featured_Stories/ultrasound_research/index.cfm
2. Fatemi M, Ogburn PL Jr, Greenleaf JF. Fetal stimulation by pulsed diagnostic ultrasound. J Ultrasound Med. 2001;20:883-9.

Tight control beneficial in Rheumatoid Arthritis (RA)

Rapid suppression of disease activity in RA correlates with reduction in joint damage. In a single-blind randomized trial involving 110 outpatients with RA of less than 5 years' duration, Glasgow researchers compared frequent, intensive treatment with routine care.1 Intensively treated patients were seen monthly by the same rheumatologist, who assessed their composite disease-activity score, injected up to three swollen joints with a steroid, and rapidly escalated disease-modifying therapy according to a predefined protocol until disease activity was controlled. Routine-care patients were assessed every 3 months with no formal measure of disease activity and received treatment at the attending rheumatologist's discretion.
The intensive-treatment group experienced significant reduction in disease-activity score, higher rates of treatment response and remission, and overall less radiologic progression compared to the routine-care patients. This improvement resulted at no additional health care cost.

1. Grigor C. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet. 2004;364:263-9.

PEEP 'into' ARDS

Ashbaugh et al. introduced the use of positive end-expiratory pressure (PEEP) during mechanical ventilation to treat hypoxemia in adult respiratory distress syndrome (ARDS).1 Later, animal models suggested two ventilator induced lung injury mechanisms: overdistention of alveoli under high pressures and shearing stress produced by repetitive opening and collapse of alveoli due to

surfactant defect in ARDS. An earlier clinical trial conducted by ARDS Clinical Trials Network (ACTN)2 demonstrated a significant survival benefit when patients received a low tidal volume (6ml / kg body weight) rather than the older regimen of 12 ml /kg.3 In the July issue of NEJM, ACTN investigated whether high PEEP levels combined with low tidal volumes prevented collapse of alveoli, minimizing stress forces and thus increasing survival. The answer they found was, 'NO'.

1. Ashbaugh DG, Bigelow DB, Petty TL, et al. Acute respiratory distress in adults. Lancet. 1967;2:319-23.

2. Brower RG. National Heart, Lung, and Blood Institute ARDS Clinical Trials Network. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med. 2004;;351:327-36.

3. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med. 2000;342:1301-8.