

EDITOR'S CHOICE

STEM CELLS: tools for screening drugs in SMA

The ability to make motor neurons from stem cells has always been an attractive prospect given the absence of any effective treatment for motor neurone disease and its variants. Over the years the developmental biologists have been hard at work understanding the normal developmental programme that specifies how a precursor cell ultimately ends up in the ventral horn as a motor neuron. This work, coupled to the exciting new development a couple of years ago on making induced pluripotent stem cells (iPS cells) has now translated into tools that might just lead to cell therapies. The group of Clive Svendsen and colleagues in Wisconsin have generated motoneurons using induced-pluripotent stem cells from a child with type 1 spinal muscular atrophy (SMA) and his unaffected mother. The clones so generated were then propagated and differentiated into motoneurons, and that whilst "iPS-SMA cells can produce similar numbers of neurons and motor neurons initially...the disease phenotype selectively hinders motor neuron production and/or increases motor neuron degeneration

at later time points". So, having set up a nice in vitro model of SMA, they screened for the ability of drugs such as tobramycin and valproic acid to increase production of the SMN protein. This ability to generate motor neurons in this way could simplistically be viewed as a way of trying to make new nerve cells to replace those that are lost in the disease. Obviously in cases where there is a genetic component such as in SMA, the cells would be expected to follow the fate of their predecessors in the host: namely die- as this paper shows in vitro. Perhaps the greatest strength of these cells is not so much as cell replacement but as a model and a cell line by which to study disease pathogenesis and then test therapeutic agents. – **RAB**

Ebert AD, Yu J, Rose FF Jr, Mattis VB, Lorson CL, Thomson JA, Svendsen CN

Induced pluripotent stem cells from a spinal muscular atrophy patient.

NATURE

2009;457:277-81.

PARKINSON'S DISEASE: watch out red heads

It seems that there has been a vague story circulating for years, that people with melanoma more frequently get Parkinson's disease... and that people with Parkinson's disease are at increased risk of melanoma...

Alberto Acherio and colleagues from Harvard decided to investigate this association at its most simple and ask: does hair colour (reflecting the quantity and distribution of melanin) influence the risk of Parkinson's? To get sufficient numbers, they ploughed the databases of the Health Professionals Follow-up Study (38,641 men) and Nurse's Health Study (93,661 women). And the result was that PD risk is 1, 1.4, 1.61, 1.93 for black, brown, blond, and red hair. For PD onset before the age of 70, there was an even greater correlation with odds

ratios of 1, 2.25, 2.73, 3.83 for the same hair tones. So, that explains why people with PD are at risk of melanomas... because they are more likely to be fair or red-haired. But why should variable expression of melanin be related to the risk of Parkinson's? Much biochemical hand-waving is the answer, from which I will spare you. No mention of sun-block preventing Parkinson's disease anywhere though, most disappointing. – **AJC**

Gao X, Simon KC, Han J, Schwarzschild MA, Ascherio A.

Genetic determinants of hair color and Parkinson's disease risk.

ANNALS OF NEUROLOGY

2009;65(1):76-82.

Journal reviewers

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HEADACHE: Glucose metabolism and headache

Despite the frequency of the problem and the volume of research, many aspects of migraine pathophysiology remain unclear. In particular we don't know what "sets the scene" for migraine, and whether there is something different about the brain of migraineurs. Looking at this question, this study is the first comparison of brain metabolism in migraineurs during headache-free intervals and controls. It examined glucose metabolism at rest in 11 migraineurs and 14 controls using PET scanning.

The study found significantly higher glucose metabolism bilaterally in the posterior subcortical cerebrum and in the cerebellum in those with migraine, during headache-free periods, compared to controls. Involvement in occipito-temporal white matter fits the clinical preponderance of visual symptoms in migraine. It is supported by electrophysiological studies showing increased amplitude of visual evoked responses in migraine, and functional studies showing heightened ability of migraine patients in low-level visual tasks, and heightened sensitivity to certain visual stimuli. The

involvement of the cerebellum is unexpected and the authors conjecture a shared link with essential tremor.

The investigators speculate whether increases in glucose metabolism are due to ischemia or a mitochondrial dysfunction. Given the frequency of migraine, this would have to be a subtle change in a biochemical property, or in metabolic processing under stress. To explain the frequency of migraine, it seems likely that any change is a variation on the biochemical spectrum, activated by other factors. Larger scale studies are important to investigate this further, preferably using functional MRI, avoiding the issue of radiation. It is intriguing, and takes us a step further in understanding possible changes in the brain of migraineurs, which predispose to the cascade of events involved in a migraine. – **HAL**

Kassab M, Bakhtar O, Wack D, Bednarczyk E.

Resting brain glucose uptake in headache-free migraineurs.

HEADACHE

2009;49:90-7.

COGNITION: Language lateralisation and the brachial plexus

Such a simple experiment this, but so profound. This German-Hungarian-American collaboration addresses how language becomes lateralised... Fifteen subjects were studied, who had all had severe brachial plexus injuries at birth so that one limb was flaccid and useless. Those subjects who had injuries to the right arm had – on fMRI testing of word generation – much greater language representation on the right hemisphere than in those with left arm injury. Furthermore, there was a correlation between the degree of injury and the extent of left-to-right shift.

This is exciting because it shows that reduced arm or hand function from a peripheral injury can lead to cortical reorganisation during language development. This implies that lateralisation depends to some extent on hand function. Perhaps our left hemisphere develops language best when we can gesticulate freely with our right hand? – **AJC**

Auer T, Pinter S, Kovacs N, Kalmar Z, Nagy F, Horvath RA, Koszo B, Kotek G, Perlaki G, Koves M, Kalman B, Komoly S, Schwarcz A, Woermann FG, Janszky J.

Does obstetric brachial plexus injury influence speech dominance?

ANNALS OF NEUROLOGY
2009;65(1):57-66.

HEADACHE: Sodium channels, migraine and epilepsy

This study links a sodium channel gene mutation with familial hemiplegic migraine and epilepsy. It reports a novel mutation in the SCN1A gene. SCN1A mutations are well known in childhood epilepsy. The gene encodes a subunit of the sodium channel, and mutations have been described since 1997 in association with severe myoclonic epilepsy of infancy and “febrile seizures plus” syndromes. Recently, two mutations have been found in patients with pure familial hemiplegic migraine.

This paper describes a Portuguese family with a SCN1A L263V mutation. Five family members had familial hemiplegic migraine, and three of these had epilepsy as well. Importantly, migraine and seizures occurred independently. This description is a clear example of a molecular link between migraine and epilepsy. Many studies, going back over more than a century, have highlighted a link between migraine and seizures clinically, but this has simply been a clinical correlation. This study extends the spectrum of disease associated with epilepsy and migraine. The mechanism of this link between familial hemiplegic migraine and seizures is uncertain, but it seems most likely that there is more than one molecular pathway involved, given the difference in time course and manifestations of a migraine and a seizure. – **HAL**

Castro M-J, Stam AH, Lemos C, de Vries B, Vanmolkot KRJ, Barros J, Terwindt GM, Frants RR, Sequeiros J, Ferrari MD, Pereira-Monteiro JM & van den Maagdenberg AMJM.

First mutation in the voltage-gated NaV1.1 subunit gene SCN1A with co-occurring familial hemiplegic migraine and epilepsy.

CEPHALALGIA
2009;29:308-13.

EPILEPSY: plumbing the sulcal depths for seizures

Some patients present with highly focal clinical seizure patterns, which make one feel that there must be some structural abnormality underlying it, but standard neuroimaging is usually depressingly normal. There is a good chance that what is being missed is a cortical dysplasia, the commonest cause of refractory focal epilepsy after mesial temporal sclerosis. A number of imaging techniques have been devised to try and identify the location of subtle lesions, missed on eyeballing the scan.

In this study the authors studied scans of 43 patients whose initial assessment had not revealed a structural cause of their seizures, using a variety of techniques, including surface rendering, curvilinear reformatting (creating slices parallel to the brain surface), texture based analysis and voxel based morphometry. When an area of FCD was indentified, they used an automated technique of sulcal extraction and went on to measure the depth of the sulci. Eighty-six percent of small FCD lesions were located at the base of the sulci and these sulci were deeper than those in normal controls. The authors discuss how this may arise. They relate the lesions to the mechanism of sulcus formation, which is thought to be due to mechanical factors generated by cortico-cortical connections and subcortical connections. There is lower cell density in FCD than in normal cortex, and they hypothesise that this, combined with altered connectivity may alter local tensions to create a deeper sulcus than normal.

The type of dysplasia found was most commonly Taylor-type dysplasia, which has a better prognosis following surgery, so it is important not to miss these cases and clinical and electrographic clues can now help target a neuroradiological search, which it would appear is more likely to bear fruit if it plumbs the sulcal depths. – **MRAM**

Besson P, Andermann F, Dubeau F, Bernasconi A.

Small focal cortical dysplasia lesions are located at the bottom of a deep sulcus.

BRAIN
2008;131:3246-55.

PARKINSONISM-DYSTONIA: a surprising connection

Just occasionally genetics can corral together the most unlikely bed-fellows. Take this work from Queen Square, in which studies of two consanguineous families have shown the cause of an adult parkinsonism-dystonia complex, which is L-dopa responsive and not associated with iron deposition, is a mutation in the 741 amino acid of a protein made by the gene snappily called PLA2G6. This turns out to be exactly the same mutation as that which causes infantile neuroaxonal dystrophy and also a subset of cases with neurodegeneration with brain iron accumulation... This all appears to make sense at a molecular level (!) when it emerges that if you replace arginine at position 741 by glutamine in both copies of the gene, then you get adult parkinsonism-dystonia complex. Whereas if you replace the arginine with a tryptophan then either neuroaxonal dystrophy or neurodegeneration with brain iron accumulation results... depending on exactly what the mutation was. Now how do we make sense of that? – **AJC**

Paisan-Ruiz C, Bhatia KP, Li A, Hernandez D, Davis M, Wood NW, Hardy J, Houlden H, Singleton A, Schneider SA.

Characterization of PLA2G6 as a locus for dystonia-parkinsonism.

ANNALS OF NEUROLOGY
2009;65(1):19-23.

PARKINSON'S PLUS: and riluzole

Perhaps it is not that surprising, but it is disappointing nonetheless: riluzole does not work in PSP and MSA. So says the phase 3 NNIPPS study, which was a three-year placebo-controlled trial of 363 PSP and 4040 MSA patients from King's, Paris and Ulm. The unexpected finding was that during the three years of follow-up, 45% of the PSP and MSA populations died, much more than you might have predicted. – **AJC**

Bensimon G, Ludolph A, Agid Y, Vidailhet M, Payan C, Leigh PN; NNIPPS Study Group.

Riluzole treatment, survival and diagnostic criteria in Parkinson plus disorders: the NNIPPS study.

BRAIN
2009;132(Pt1):156-71.
Epub 2008 Nov 23.