miRNA and ASO – The initial approach to treating genetic diseases in a new way

One of the holy grails of treating genetic disorders of the CNS is to target the abnormal gene itself and by so doing effect a cure without having to worry about off target effects. There have been two recent papers which are worth highlighting in this regard – one using a microRNA approach, the other an antisense oligonucleotide (ASO) strategy and both involving autosomal dominant trinucleotide repeat disorders.

In the first paper by Miyazaki et al in Nature Medicine (with a wonderfully clear News and Views commentary on it by Christopher Pearson), they concentrated on spinal bulbar muscular atrophy (SBMA) which is a slowly progressive lower motor neuron disorder of men. The disease is characterised by a CAG expansion in the androgen receptor, which then causes motor neuronal cell dysfunction and death through translocation of the mutant receptor within the cell. This has in the past led to attempts to block translocation using anti-androgen agents, although as a clinical therapy this creates obvious problems. In this new paper the authors looked at a transgenic model of this condition and found that one endogenous microRNAs in particular (the imaginatively named miRNA-196a) was upregulated and that by overexpressing it they could slow down the disease process. This they did using an AAV delivery system that selectively targeted the motoneurons. They then showed that miR-196a mediated its effects on the mutant receptor through a protein that is involved with mRNA processing (CELF2). This beautiful work shows how miRNAs are coming of age not only in terms of how they regulate networks of intracellular processes but how they can be recruited for treating disease.

In the second study the disease under attack is Huntington’s disease, which has its CAG repeat in exon 1 of the huntingtin (Htt) gene. This gene product causes extensive cell loss in the CNS but typically not until patients are in their 40s, although exactly when the disease process begins relative to clinical expression remains a subject of great interest (see TRACK-HD and PRECIT-HD studies). Obviously being able to switch off the mutant gene (mHtt) whilst leaving the normal hit to do its job has proven difficult, as has getting the silencing agent for the mutant hit in all cells for long period of times. This last point in particular has vexed the field but a recent paper by Kordasiewicz et al in Neuron (again accompanied by a lovely Preview by Lu and Yang) suggests that this might not be necessary as they showed that transiently knocking down mHtt could have long lasting benefits in animal models of disease. This implies that stopping the production of mHtt even if only for a short time may allow the cell to recover, regroup and fight another day and thus whilst repeated injections of ASOs may be required, the frequency of administration may be less than once thought.

These papers highlight once more the skill of researchers to get to the heart of disease, and their ingenuity in how to do this. Obviously the challenge still remains as to how one can translate such findings into a much larger, longer living human patient – but slowly we are moving towards therapies that seek to truly switch off disease causing genes and their products.

– Roger Barker, Cambridge Centre for Brain Repair

Pearson CE. Co-opting endogenous microRNAs for therapy.
Miyazaki Y, Adachi H, Katsuno M et al. Viral delivery of miR-196a ameliorates the SBMA phenotype via the silencing of CELF2.
NATURE MEDICINE 2012;18:1136-1141.
Kordasiewicz HB, Stanek LM, Wancewicz EV et al. Sustained Therapeutic Reversal of Huntington’s Disease by Transient Repression of Huntington Synthesis.
NEURON 2012;74:1031-44.

Intramuscular midazolam for status epilepticus

Large studies of status epilepticus which change practice are hard to come by but this is one such. The study compared the outcome of treatment of status epilepticus with IM midazolam and IV lorazepam, which has been the gold standard since 1998. This massive effort included 3114 paramedics and 73 hospitals. Children estimated to be over 13kg and adults were included and were treated if convulsive seizures had been continuing for over five minutes. Patients were excluded with major trauma, hypoglycaemia, cardiac arrest or HCR40. Essentially the question is does speed of access with an IM injection of midazolam 10mg in adults, using an autoinjector make up for speed of distribution of IV access of IV lorazepam 4mg (smaller doses were given to little people) given also that it is a different drug being administered. The short
answer to the question is yes, which means that we should be looking to change practice for emergency management to IM midazolam.

The primary outcome of the study was termination of seizures before arrival in the emergency department without the need for the paramedics to provide rescue therapy. The key secondary outcome was time from opening the box containing treatment to the termination of seizures. 448 patients were assigned to IM midazolam of whom 443 received the drug. 445 were assigned to IV lorazepam of whom 297 received the drug. Of the remainder, seizures stopped anyway in 55, before the drug was given and in 42 IV access could not be achieved. In the intention to treat analysis, treatment failure occurred in 26.6% of midazolam patients and 36.6% of lorazepam patients. Per protocol figures were 25.1% and 35.7% respectively. Midazolam also fared better on all secondary measures, except slightly longer hospital stays. Seizure recurrence within 12 hours was similar and only around 10% in both groups and hypotension was also similar. Although the time from giving the injection to cessation of seizures was slightly longer with midazolam, this was more than relative speed of IM access compared with IV access for lorazepam. The authors cautiously state that IM midazolam is non-inferior to IV lorazepam. With these data one might go further.

~ Mark Manford, Addenbrooke’s and Bedford Hospitals.

Infection and autoimmunity – an overlap in the brain?
NMDAR-receptor antibody related encephalitis is now a well-recognised, clinically distinctive condition often seen in younger individuals with a good response to immunotherapies. Patients frequently develops fever and headache prior to, or during, their illness. Importantly, the antibodies are of the IgG class.

Pruss et al retrospectively show antibodies of IgG, IgA and IgM classes which are directed against the NMDA receptor in 13 of 44 (30%) patients with proven HSV encephalitis (HSVE). The diagnosis of HSVE appears robust in that patients had the typical symptoms of HSV infection and the NMDA classes were never detected. Another case had serum NMDAR-IgA after around one year but serum NMDAR-IgG or CSF NMDAR-IgA/M were never detected. Case reports and small series of patients support the hypothesis that the inhibition of lactate transport by NMDAR-IgA antibodies may catecholaminergic neurotransmission. The presence of these antibodies in the setting of HSVE is intriguing, their role remains unclear. Nevertheless, these antibodies should certainly be measured in a prospectively collected series of HSVE.

These data provide one potential rationale for the use of steroids in HSVE. They also suggest that infectious and autoimmune encephalitis may coexist. Although headache, fever and cognitive deficits do overlap, there are marked differences between many clinical and paraclinical features of HSVE and ‘typical’ NMDAR-IgG antibody encephalitis. The presence of these antibodies in the setting of HSVE is intriguing, their role remains unclear. Nevertheless, these antibodies should certainly be measured in a prospectively collected series of HSVE. Reproducible findings may mean that in the future steroids are routinely added to acyclovir in the setting of HSVE.

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Pruss H, Finke C, Höltje M, et al. NMDA receptor antibodies in herpes simplex encephalitis. ANNALS OF NEUROLOGY. Accepted manuscript online: 16 JUL 2012. DOI: 10.1002/ana.23689.