Future NEUROLOGY

BULLETIN BOARD

HDAC5: a key factor in nerve regeneration

A group from Washington have identified the HDAC5 protein as a key component in the reaction that induces nerve regeneration.

A paper published in a recent issue of *Cell* has identified HDAC5 protein as a key component in the chain reaction that induces nerve regeneration. The group from Washington University (MO, USA) who are responsible for the paper, hope this finding will contribute to nerve regeneration being used to treat CNS injuries.

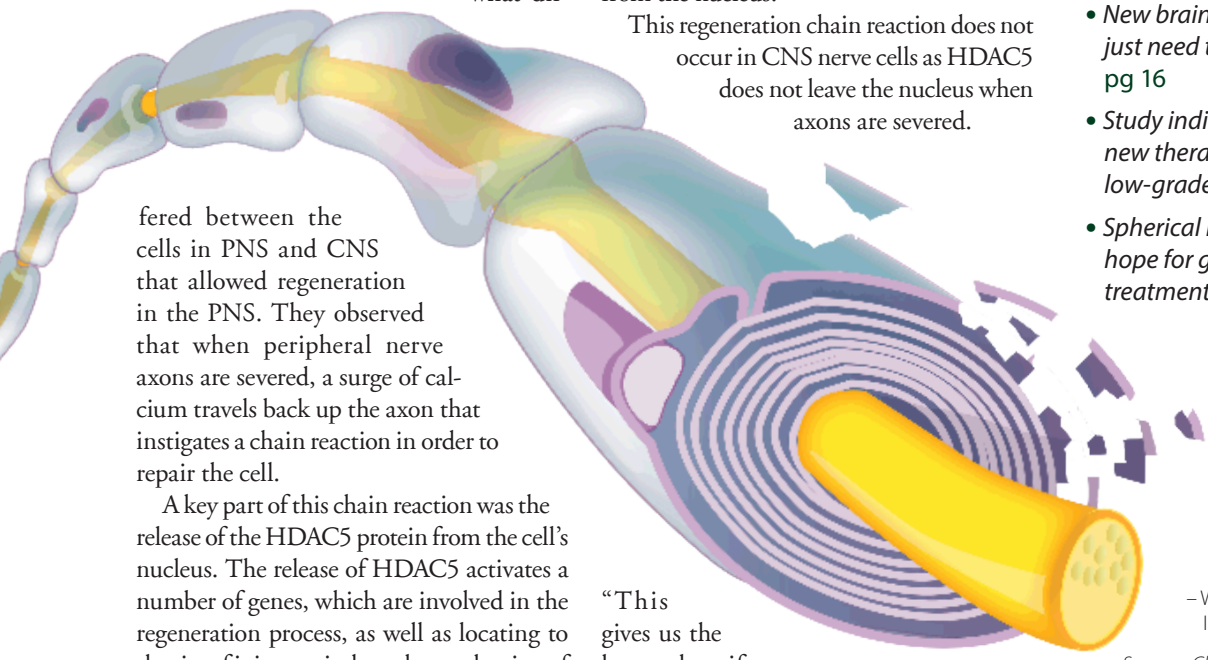
Although some nerve cells in the PNS have been shown to regenerate damaged axons, injured nerve cells in the CNS – the brain and spinal cord – typically do not replace lost axons. The group tried to identify what differed between the cells in PNS and CNS that allowed regeneration in the PNS. They observed that when peripheral nerve axons are severed, a surge of calcium travels back up the axon that instigates a chain reaction in order to repair the cell.

A key part of this chain reaction was the release of the HDAC5 protein from the cell's nucleus. The release of HDAC5 activates a number of genes, which are involved in the regeneration process, as well as locating to the site of injury to induce the production of microtubules. As part of the cytoskeleteon, microtubules are rigid tubes that support the structural network of nerve cells and they also help to establish the structure of axons.

Valeria Cavalli, Assistant Professor of neurobiology at Washington University and senior author of the paper, said "We knew several genes that contribute to the regrowth of these nerve cell branches, which are called axons, but until now we didn't know what activated the expression of these genes and, hence, the repair process."

The group extended their investigation by genetically modifying peripheral nerve cells so that it did not release the HDAC5 protein from the nucleus. These cells did not regenerate *in vitro* after they were damaged. In addition, axon regrowth was encouraged *in vivo* when animals were given drugs that increased the level of HDAC5 being released from the nucleus.

This regeneration chain reaction does not occur in CNS nerve cells as HDAC5 does not leave the nucleus when axons are severed.



"This gives us the hope that if we can find ways to manipulate this system in brain and spinal cord neurons, we can help the cells of the CNS regrow lost branches. "We're working on that now", concluded Cavalli. "This puts us a step closer to one day being able to develop treatments that enhance axon regrowth."

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– Written by Theo Bond
Illustration by Hannah Morton

Sources: Cho Y, Sloutsky R, Naegle K, Cavalli V. Injury-induced HDAC5 nuclear export is essential for axon regeneration. Cell *155(4), 894–908 (2013); Washington University press release: https://news.wustl.edu/news/Pages/26108.aspx*

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Strategic alliance announced for neurometabolomics research

Agilent Technologies have announced a collaboration with Daegu Gyeongbuk Institute of Science and Technology for neurometabolomics research.

"The Neurometabolomics Excellence Research Center will help sharpen South Korea's edge in brain science and allow Daegu Gyeongbuk Institute of Science and Technology to contribute significantly to world-leading research."

Agilent Technologies (Berkshire, UK), a global measurement specialist company, and Daegu Gyeongbuk Institute of Science and Technology (DGIST; Daegu, South Korea), a government-funded institute, have recently announced that they are collaborating for neurometabolomics research.

The collaboration will see DGIST's new research center utilize Agilent Technologies' bioanalytical instruments to identify biomarkers for detection and diagnosis of brain diseases.

Eun-Kyoung Kim, DGIST research center director, commented on the collaboration, "The Neurometabolomics Excellence Research Center will help sharpen South Korea's edge in brain science and allow DGIST to contribute significantly to world-leading research." Kim continued, "By working with Agilent, we can continue to spearhead developments and research in brain science."

Rod Minett, general manager of Agilent Technologies' life sciences business in South Korea and the South Asia Pacific region, explained the importance of the collaboration, "The brain is arguably the most important organ in the human body, and Agilent supports the quest to help scientific and medical communities further neuroscience discovery for the good of mankind."

–Written by Jessica Thorne

Source: Agilent Technologies and Daegu Gyeongbuk Institute of Science and Technology collaborate on neurometabolomics research: www.agilent.com/about/newsroom/presrel/2013/25oct-ca13075.html

Biomarkers could predict occurrence of Alzheimer's disease

Researchers have reported the use of biomarkers to detect cognitive decline.

A group of researchers from John Hopkins University School of Medicine (MD, USA) have recently discovered that certain proteins in cerebral spinal fluid can predict cognitive decline, a symptom associated with the progression to Alzheimer's disease (AD).

Lead researcher, Marilyn Albert ex plained the initiative behind the research, "We wondered if we could measure something in the cerebral spinal fluid when people are cognitively normal to give us some idea of when they will develop difficulty," Albert continued, "The answer is yes."

The study tested cerebral spinal fluid from samples collected over 10 years from the Biomarkers for Older Controls at Risk for Dementia project. This involved testing samples from 265 middle-aged healthy volunteers, in which three-quarters had a family history of AD.

The team measured the baseline ratio of two proteins, phosphorylated tau and β-amyloid, in cerebral spinal fluid, which for several years have been known to have an association with advanced AD. It was reported that the ratio of these proteins can indicate whether a patient would develop AD 5 years before the

onset of cognitive impairment. In addition, the team reported that the rate at which the levels of these two proteins changed was also predictive. Higher levels of phosphorylated tau, compared with that of phosphorylated β-amyloid, led to an increased probability of symptoms developing.

Although further validation is still required, if proven, this study could provide a guide to developing early drug treatments for the disease. In addition, this discovery could also be used to test drugs currently in the pipeline to observe whether they can reduce the levels of these two proteins.

–Written by Jessica Thorne

Source: Johns Hopkins researchers identify biomarkers in spinal fluid: www.hopkinsmedicine.org/news/media/releases/finding_alzheimers_disease_before_symptoms_start

GW Pharmaceuticals announce Phase Ib/IIa clinical trial for the treatment of recurrent glioblastoma multiforme

The multicenter study will assess the safety and tolerability of cannabinoids for the treatment of recurrent glioblastoma multiforme.

GW Pharmaceuticals plc (Salisbury, UK) has announced that it has commenced a Phase Ib/IIa clinical trial for the treatment of recurrent glioblastoma multiforme (GBM).

GBM, a particularly aggressive tumor that forms from abnormal growth of glial tissue, accounts for approximately 50% of the 22,500 new cases of brain cancer diagnosed in the USA each year. Currently, treatment options are limited, with expected survival a little over 1 year. This is considered a rare, or orphan, disease by the US FDA and the EMA.

The current study follows several years of preclinical research conducted by GW in the field of glioma, which has demonstrated that cannabinoids inhibit the viability of glioma cells both *in vitro* and *in vivo* via apoptosis, may affect angiogenesis, and has demonstrated tumor growth-inhibiting action and an improvement in the therapeutic efficacy of temozolomide, a standard treatment for glioma. In addition, GW have published results that suggest that tumor response is positively associated with tissue levels of cannabinoids. Research has also identified the putative mechanism of action for the cannabinoid product candidate, where autophagy and programmed cell death are stimulated via stimulation of the TRB3 pathway.

Discussing the study, Stephen Wright (from GW Pharmaceuticals) commented: "We are very excited about moving this compound into further human study and the prospects of cannabinoids as new anti-cancer treatments. This is GW's first clinical study of cannabinoids as a potential treatment to inhibit tumor growth." Wright continued: "We believe this clinical program demonstrates the flexibility and broad application of GW's cannabinoid platform to treat significant, unmet therapeutic needs."

The study is a 20-patient, multicenter, two-part study with an open-label phase to assess the safety and tolerability of GW cannabinoids in combination with temozolomide, and a double-blind, randomized, placebo-controlled phase with patients

"...this clinical program demonstrates the flexibility and broad application of GW's cannabinoid platform to treat significant, unmet therapeutic needs."

randomized to either active treatment or placebo, and with a primary outcome measure of 6-month progression-free survival. The objective of the study is to assess the tolerability, safety and pharmacodynamics of a mixture of two principal cannabinoids, THC and CBD in a 1:1 allocation ratio, in combination with temozolomide in patients with recurrent GBM. Secondary end points include additional pharmacokinetic and biomarker analyses and additional measurable outcomes of tumor response.

– Written by Dominic Chamberlain

Source: GW Pharmaceuticals press release: www.gwpharm.com/GW%20Pharmaceuticals%20Commences%20Phase%201b2a%20Clinical%20Trial%20%20for%20the%20Treatment%20of%20Glioblastoma%20Multiforme%20GBM.aspx

New brain cancer treatment: do we just need to TWEAK our approach?

A study led by the Translational Genomics Research Institute (AZ, USA) suggests that a cellular pathway interaction known as TWEAK–Fn14, often associated with the repair of acute injuries, may also be a viable target for drug therapy to the spread of cancer, especially to the brain.

TWEAK, a cytokine, or soluble protein, controls many cellular activities and acts by binding to the Fn14 cell surface receptor. This triggers a wide range of cellular activities, including blood clotting, inflammation, cell proliferation, cell migration and the creation of new blood vessels.

While many of the associated activities are beneficial, such as healing cuts, excessive TWEAK–Fn14 activation has also been linked to tissue damage and degradation, including autoimmune diseases, and the survival, migration and invasion of cancer cells.

Discussing the study, Associate Professor Nhan Tran (Translational Genomics Research Institute), commented "Our results show that the TWEAK–Fn14 interaction is a viable drug target, and they provide the foundation for further exploration of this system in researching invasive cancers," Tran continued: "Because of its unique qualities and association with acute injuries, this drug-like molecule not only could benefit cancer patients, but also might be applied to patients with autoimmunity, heart disease, such as atherosclerosis, and rheumatoid arthritis."

Overexpression of TWEAK–Fn14 has been linked to several types of cancer including breast, pancreatic, esophageal, lung, liver and glioblastoma.

Using protein–protein docking models, the team selected 129 small molecules for screening, which identified four that inhibited the binding of TWEAK to Fn14.

The study concluded that one compound in particular, L524-0366, "completely suppressed TWEAK-induced glioma cell migration without any potential cytotoxic effects."

Further discussing the study, Michael Berens, Deputy Director for Research Resources, Director of the Translational Genomics Research Institute's Cancer and Cell Biology Division and coauthor of the study stated: "These results represent a significant step towards proving that the TWEAK–Fn14 interaction may be key to treating invasive glioblastoma brain tumors," adding that "The next step will be to move this compound forward for drug development and eventual testing in clinical trials, where it might bring immediate benefit for patients."

"These results represent a significant step towards proving that the TWEAK–Fn14 interaction may be key to treating invasive glioblastoma brain tumors."

– Written by Dominic Chamberlain

Source: Translational Genomics Research Institute press release: www.tgen.org/news/2013-media-releases/tgen-study-shows-tweak-fn14-is-drug-target-for-cancer.aspx#.UopFn9xFAnw

Study indicates that mTOR may be a new therapeutic target in pediatric low-grade gliomas

Findings published online this week in the journal *Neuro-Oncology* indicate that a known genetic pathway may represent a therapeutic target in many pediatric low-grade gliomas. These brain tumors represent the most common CNS malignancies in children, the treatment of which can often cause serious side effects.

"Even though these tumors are considered 'low grade' and not particularly aggressive, many patients suffer severe, life-altering symptoms, so we desperately need better therapies," commented Eric Raabe of the Johns Hopkins Kimmel Cancer Center (MD, USA) and coauthor of this new study. Following on from previous studies that implicated the mTOR signaling pathway in such malignancies, Raabe and colleagues analyzed tissue samples from 177 pediatric low-grade gliomas using immunohistochemistry. They scrutinized several tumor subtypes, including the most common manifestation of pediatric low-grade glioma, termed pilocytic astrocytomas. This pathway signals through two protein complexes, termed mTORC1 and mTORC2, and can promote increased cell survival and growth. The mTOR signaling cascade is known to be active in many cancers, and inhibitory agents such as rapamycin are widely available.

mTORC1 activity was noted in 90% of the low-grade gliomas studied, while 81% demonstrated both mTORC1 and mTORC2 activity. Interestingly, mTOR activity was more common in tumors that originated from the optic pathway, compared with those from other areas of the brain. Further to their investigation of tumor samples, the team also tested an investigational mTOR inhibitor MK-8669, also known as ridaforolimus, in two pediatric low-grade glioma cell lines. In one cell line, the agent reduced cell growth by up to 73% over 6 days, and decreased cell growth up to 21% in 4 days in the other cell line.

"We think mTOR could function as an Achilles' heel," explained Raabe. "It drives cancer growth, but when mTOR is inhibited, the tumor falls apart."

The study suggests that mTOR may be a suitable target for pharmacologic blockade in these common childhood tumors, although the efficacy of treatment may vary with tumor subtype. The investigators hope to build on this research by further investigating their findings in animal models of low-grade glioma and also plan to test the efficacy of additional inhibitory agents.

–Written by Emily Brown

Sources: Hütt-Cabezas M, Karajannis MA, Zagzag D et al. Activation of mTORC1/mTORC2 signaling in pediatric low-grade glioma and pilocytic astrocytoma reveals mTOR as a therapeutic target. Neuro-Oncology *doi:10.1093/neuonc/not132 (2013) (Epub ahead of print); Johns Hopkins Medicine press release: www.hopkinsmedicine.org/news/media/releases/common_genetic_pathway_could_be_conduit_to_pediatric_tumor_treatment*

"mTORC1 activity was noted in 90% of the low-grade gliomas studied, while 81% demonstrated both mTORC1 and mTORC2 activity."

Spherical nucleic acids provide hope for glioblastoma multiforme treatment

Glioblastoma multiforme (GBM) is the most common and lethal brain tumor in adults, accounting for over half of all functional tissue brain tumors and 20% of intracranial tumors, with a survival rate of 14–16 months after diagnosis. There are many known genes implicated in the development of this lethal disease; however, efficient therapies and delivery

methods to target them have been lacking, rendering GBM currently incurable.

Samuel Jensen and colleagues (Northwestern Brain Tumor Institute, IL, USA) therefore set out to investigate a novel method of delivery of a drug to a specific gene (*BCL2L12*) known to be involved in GBM. This method consisted of delivering RNAi-based spherical nuclear acids (SNAs) to the brain, where they switched off the *BCL2L12* gene. These SNAs consisted of gold nanoparticles joined to siRNA duplexes that targeted the *Bcl2L12* gene.

The results published recently in *Science Translational Medicine* indicated that SNAs successfully penetrated the blood–brain and blood–tumor barriers, and were shown to reduce both BCL2L12 mRNA and protein levels. Delivery of the molecule increased tumor apoptosis and reduced tumor burden and progression in mice with GBM. The survival rate increased by nearly 20% and tumor size was reduced three-to-four-fold, clearly demonstrating the effectiveness of the delivery method.

Thus, silencing this (and potentially other) genes could increase the efficacy of existing conventional chemotherapeutic treatments for GBM, which currently often fail. In addition, this first demonstration of nanostructures being injected and successfully delivering their therapeutic molecule to the brain indicates that this general technique could be applied to a wide range of other diseases in the future.

"The RNA interfering-based SNAs are a completely novel approach in thinking about cancer therapy," commented Alexander Stegh (Northwestern University), senior coauthor of the study. "One of the problems is that we have large lists of genes that are somehow disregulated in glioblastoma, but we have absolutely no way of targeting all of them using standard pharmacological approaches. That's where we think nanomaterials can play a fundamental role in allowing us to implement the concept of personalized medicine in cancer therapy."

–Written by Luke Worley

Source: Northwestern University press release: www.northwestern.edu/newscenter/stories/2013/10/incurable-brain-cancer-gene-is-silenced.html#sthash.tOx6p8v2.dpuf

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