Mention of Hes1 and Ascl1 in the following article as factors for neural stem cell activation was noteworthy because our algorithmic quantum biology modeling had identified calcineurin as a factor for the activation.

Given this fact, our modeling was applied to Hes1 and Ascl1 to determine if these epigenetic activities could be linked to calcineurin.

The results were affirmative and the findings are outlined in the documents affixed to this article for review by qualified bioinformatic professionals for discussion with MCFIP.

https://www.sciencedaily.com/releases/2019/05/190510094811.htm

Prince Charming's kiss unlocking brain's regenerative potential?

Kyoto University identifies 'wake-up' signal for deep-sleeping neural stem cells

Date:

May 10, 2019

Source:

Kyoto University

Summary:

Researchers find that 'waves' of Hes1 and Ascl1 gene expression control the quiescent and active state of adult neural stem cells. Hes1 expression promotes quiescence and suppresses Ascl1, and knocking out Hes1 increases Ascl1 expression and subsequent adult neural stem cell activation.

The human body has powerful healing abilities. But treating brain disorders is no easy task, as brain cells -- neurons -- have limited ability to regenerate. Nonetheless, stem cells are a form of natural backup, a vestige of our days as still-developing embryos.

The difficulty is that, as we age, our brains' stem cells 'fall asleep' and become harder to wake up when repairs are needed. Despite efforts to harness these cells to treat neurological damage, scientists have until recently been unsuccessful in decoding the underlying 'sleep' mechanism.

Now, researchers at Kyoto University studying brain chemistry in mice have revealed the ebb and flow of gene expression that may wake neural stem cells from their slumber. These findings, which may also apply to stem cells elsewhere in the body, were recently published in the journal *Genes & Development*.

"No one before us has directly compared active stem cells in embryos with inactive, 'quiescent' adult stem cells," says group leader Ryoichiro Kageyama of Kyoto University's Institute for Frontier Life and Medical Sciences, who points out that at least two genes and their associated proteins regulating activation had already been identified.

The team focused their attention on protein **'Hes1'**, which is strongly expressed in the adult cells. This normally suppresses the production of other proteins such as **'Ascl1'**, small amounts of which are periodically produced by active stem cells.

Monitoring the production of the two proteins over time, the team pinpointed a wave-like pattern that leads to stem cells waking up and turning into neurons in the brain.

When they 'knocked out' the genetic code needed to make Hes1, the cells started to make more Ascl1, which then activated almost all the neural stem cells.

"It is key that the same genes are responsible for both the active and quiescent states of these stem cells," Kageyama adds. "Only the expression dynamics differ between the two."

"A better understanding of the regulatory mechanisms of these different expression dynamics could allow us to switch the dormant cells on as part of a treatment for a range of neurological disorders."

Story Source:

Materials provided by **Kyoto University**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Risa Sueda, Itaru Imayoshi, Yukiko Harima, Ryoichiro Kageyama. **High Hes1 expression and resultant Ascl1 suppression regulate quiescent vs. active neural stem cells in the adult mouse brain**. *Genes & Development*, 2019; 33 (9-10): 511 DOI: 10.1101/gad.323196.118

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The following is provided for discussion purposes with qualified bioinformatics professionals.

TNF Epigenetic Constituents (Cell Alignment)
For Discussion Purposes

TNF-Alpha (Calnexin) Density
Calcium – threonine – magnesium (BRCA1)
Calcium – serine – magnesium (BRCA2)
Calcium – cysteine - magnesium (BRCA3)
For Discussion:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3436948/

TNF-Beta (Calmodulin) Motility
Calcium – phenylalanine – magnesium (HRas)
Calcium – tyrosine – magnesium (KRas)
Calcium – tryptophan – magnesium (NRas)

TNF-Gamma (Calcineurin)
Calcium – serine – zinc
Calcium – cysteine – zinc
Calcium – threonine – zinc

The following are examples of bioidentical "enzymes" that have evolved with various designations; e.g. AKT, mTOR, PTEN, NF-kB, and MYC.

https://medicalxpress.com/news/2019-03-scientists-id-metabolic-heart-failure.html

Bioinformatic search has, with near certainty, identified ASCL1 - 3 as being bioidentical to calcium binding and zinc finger formed calcineurin with the amino acids being threonine - serine and cysteine.

Data mining will correlate ASCL activities with calcineurin. DIY!

MARCH 26, 2019

Scientists ID new metabolic target to prevent, treat heart failure at earliest stage

by Ohio State University Medical Center

Researchers with The Ohio State University College of Medicine and The Ohio State University Wexner Medical Center have identified a metabolic process in the heart that, if treated, could someday prevent or slow the progression of heart failure.

The American Heart Association journal *Circulation* published the findings today.

Before any physical signs or symptoms of heart failure are present, the first maladaptive changes occur in cardiac cell metabolism—how the heart fuels itself to pump blood through the body constantly.

"Our hearts burn fuel, much like combustion engines in cars. Instead of gasoline, our heart cells burn fats and a small amount of glucose," said Doug Lewandowski, director of translational research at Ohio State's Dorothy M. Davis Heart and Lung Research Institute. "When our hearts become chronically stressed, they try to adapt, but some of those changes make things worse."

For their research, Lewandowski's team examined both mouse models of heart failure and human heart tissue obtained from heart failure patients before and after heart assist devices were surgically implanted. They found that the amount of a reactive fat compound, called acyl-CoA, is nearly 60 percent lower in failing hearts compared to normal hearts. This disruption in the heart's normal metabolism creates toxic fats that impair the heart's ability to function and pump properly.

Then the team tested mice that overexpressed a gene for a protein called ACSL1, that's known to make acyl-CoA. When exposed to conditions that cause heart failure, the mice kept making normal amounts of acyl-CoA and the extent of heart failure was reduced and delayed.

"By maintaining this fat compound, acyl-CoA, the hearts retained their ability to burn fat and generate energy. Importantly, overexpression of ACSL1 also reduced toxic fats, normalized cell function and reduced the progressive loss of function in the enlarged

mouse hearts," said Lewandowski, who is also a professor of internal medicine at Ohio State's College of Medicine.

When the team examined failing human hearts that had the help of a left ventricular assist device (LVAD), they found similar effects—the levels of acyl-CoA had restored to normal when the sick hearts didn't have to work beyond their capacity.

"This tells us there's an important relationship between fat metabolism in the heart and the inability to pump well, and we need to learn more. We believe targeting the normalization of acyl-CoA through gene or drug therapy or, potentially, dietary protocols, is a new approach to explore," Lewandowski said.

"Heart failure is the only form of heart disease that hasn't dropped in 35 years. As findings like these help identify the metabolic underpinnings of the disease, it gives hope for promising new therapies for patients," said Dr. K. Craig Kent, dean of the College of Medicine.

Next, Lewandowski's team wants to explore how normalizing acyl-CoA helps reduce toxic fats and increase protective fats inside the heart. Soon, they hope to use advanced imaging to track fat metabolism and function in patients' hearts.

"We need to understand how we're manipulating the chemical reactions and what exactly is leading to the improvement. Then we can look at whether we can supply the heart with fats, supplements or medications that assist with creating acyl-CoA. Ultimately, it's about trying to prevent or slow the progression toward heart failure," Lewandowski said.

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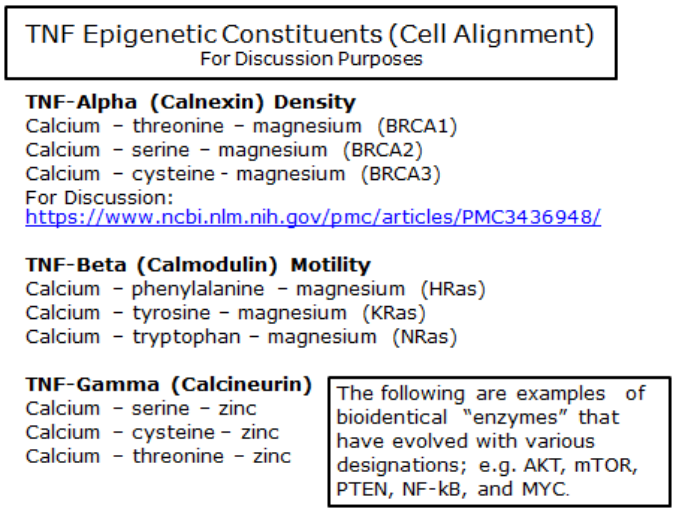
Efforts to correlate all of the interfaces described in the article relative to their potential impact on amyloid beta utilizing quantum biology modeling have been set aside.

Instead, the focus has been placed on information relative to HES1 that will likely be beneficial for future research has included the following:

- A large volume of studies verify hes1 and the Notch signaling pathway as interfacing.
- HES1 has two other members that interact; HES1 and HES3. All members can be identified as calcium binding and zinc finger formed with the amino acids being threonine - serine and cysteine.

The configuration can be verified through bioinformatic search as being calcineurin.
Refer to the following:



Data mining will correlate HES activities with calcineurin as well as the Notch pathway. DIY!

ScienceDaily
Your source for the latest research news

Web address:
http://www.sciencedaily.com/releases/2012/07/120730214110.htm

Blocking the Effects of Amyloid B in Alzheimer's Disease

ScienceDaily (July 27, 2012) — During Alzheimer's disease, 'plaques' of amyloid beta (Ab) and tau protein 'tangles' develop in the brain, leading to the death of brain cells and disruption of chemical signaling between neurons. This leads to loss of memory, mood changes, and difficulties with reasoning. New research published in BioMed Central's open access journal Alzheimer's Research & Therapy, has found that up-regulating the gene Hes1 largely counteracted the effects of Ab on neurons, including preventing cell death, and on GABAergic signaling.

The exact mechanism behind how Ab contributes to Alzheimer's disease is not yet fully understood, however researchers from Centro Andaluz de Biología Molecular y Medicina Regenerativa (CABIMER) in Spain recently discovered that Ab interferes with the normal

activity of nerve growth factor (NGF). One of the actions of NGF is activating the protein Hes1, a transcription factor required to turn on other genes. Without this factor GABAergic signaling within the brain decreases.

Using gene therapy techniques, Pedro Chacón and Alfredo Rodríguez-Tébar augmented the amount of Hes1 in cultured neurons. Increasing the amount of Hes1, directly or by activating the protein NF-kB (which in turn up-regulate the cell's own Hes1), abolished the effect of Ab and prevented neuron death. Additionally another growth factor, TGFb, which can also activate NF-kB, was able to prevent the effects of Ab on neurons by improving levels of Hes1.

Pedro Chacón explained, "Ab usually decreases the length of dendrites and GABAergic connectivity of neurons, however these effects were completely reversed by Hes1, NF-kB, and TGFb. When we grew neurons in a concentration of Ab which normally kills most cells, 50% of the neurons with extra Hes1 were able to survive."

These results demonstrate that neurons can be protected from the effects of Ab by increasing the amount of Hes1 in the cells. By clarifying the roles of NGF or TGFb in Hes1 protection this research provides strategies for limiting the effects of Alzheimer's disease.