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Two proteins work together to help cells eliminate trash; Parkinson's may result

Two proteins that share the ability to help cells deal with their trash appear to need each other to do their jobs and when they don't connect, it appears to contribute to development of Parkinson's disease, scientists report.

Much like a community's network for garbage handling, cells also have garbage sites called lysosomes, where proteins, which are functioning badly because of age or other reasons, go for degradation and potential recycling, said Dr. Wen-Cheng Xiong, developmental neurobiologist and Weiss Research Professor at the Medical College of Georgia at Georgia Regents University.

Inside lysosomes, other proteins, called proteases, help cut up proteins that can no longer do their job and enable salvaging of things like precious amino acids. It's a normal cell degradation process called autophagy that actually helps cells survive and is particularly important in cells such as neurons, which regenerate extremely slowly, said Xiong, corresponding author of the study in *The Journal of Neuroscience*.

Key to the process -- and as scientists have shown, to each other -- are two more proteins, VPS35 and Lamp2a. VPS35 is essential for retrieving membrane proteins vital to cell function. Levels naturally decrease with age, and mutations in the VPS35 gene have been found in patients with a rare form of Parkinson's. VPS35 also is a critical part of a protein complex called a retromer, which has a major role in recycling inside cells. Lamp2a enables unfit proteins to be chewed up and degraded inside lysosomes.

If the two sound like a natural couple, scientists now have more evidence that they are. They have shown that without VPS35 to retrieve Lamp2a from the trash site for reuse, Lamp2a, or lysosomal-associated membrane protein 2, will be degraded and its vital function lost.

When the scientists generated VPS35-deficient mice, the mice exhibited Parkinson's-like deficits, including impaired motor control. When they looked further, they found the lysosomes inside dopamine neurons, which are targets in Parkinson's, didn't function properly in the mice. In fact, without VPS35, the degradation of Lamp2a itself is accelerated. Consequently, yet another protein, alpha-synuclein, which is normally destroyed by Lamp2a, is increased. Alpha-synuclein is a major component of abnormal protein clumps, called Lewy bodies, found in the brains of patients with Parkinson's.

"If alpha-synuclein is not degraded, it just accumulates. If VPS35 function is normal, we won't see its accumulation," Xiong said.

Conversely, when MCG scientists increased expression of Lamp2a in the dopamine neurons of the VPS35-deficient mice, alpha-synuclein levels were reduced, a finding that further supports

the linkage of the three proteins in the essential ability of the neurons to deal with undesirables in their lysosomes.

Without lamp2a, dopamine neurons essentially start producing more garbage rather than eliminating it. Recycling of valuables such as amino acids basically stops, and alpha-synuclein is free to roam to other places in the cell or other brain regions where it can damage still viable proteins.

The bottom line is dopamine neurons are lost instead of preserved. Brain scans document the empty spaces where neurons used to be in patients with neurodegenerative diseases such as Parkinson's and Alzheimer's. One of the many problems with treatment of these diseases is that by the time the empty spaces and sometimes the associated symptoms are apparent, much damage has occurred, Xiong said.

Putting these pieces together provides several new, early targets for disease intervention. "Everything is linked," Xiong said.

Dopamine is a brain chemical with many roles, including motor control, and patients with Parkinson's have a loss of the neurons that secrete this neurotransmitter. At least in mice, VPS35 is naturally expressed in dopamine neurons in areas of the brain affected by Parkinson's.

Xiong and her colleagues reported in 2011 that reduced expression of VPS35 enables activity of the dormant-in-healthy-adults protein BACE1 to increase along with accumulation of the brain plaque that is a hallmark of Alzheimer's. Xiong said then that impaired VPS35 function likely also was a factor in Parkinson's.

In a definite vicious circle, trash starts overwhelming the brain cell's natural garbage disposal system. Proteins start getting misfolded and dysfunctional, potentially destructive proteins such as BACE1 and Lamp2a end up in the wrong place and get activated/inactivated, while good proteins get chopped up and/or bad proteins accumulate.

Parkinson's disease is characterized by uncontrolled shaking, an unstable gait and cognitive loss.

Turning back the cellular clock

Research suggests we do not yet have the whole story about how fertilized eggs produce the many different types of cell that make up our adult bodies.

It is widely accepted that an enzyme called Tet plays an important role, but something else seems to be at play, according to results published in *Nature Cell Biology*.

One of the key steps in giving a cell its identity is the addition of biological "dimmer switches," called methyl groups, which sit on the surface of its DNA and turn genes "up" or "down." Together, these methyl group markers tell each cell what its specific role is -- be that as a heart, skin or brain cell.

One of the few cell types that can add and remove their methyl groups naturally is a fertilized egg, formed when a sperm and egg fuse together. By removing methyl groups from the sperm and egg, the fertilized cell becomes a blank canvas. As it grows into an embryo, new methyl groups are added onto the DNA of these embryonic cells. By adding them in different places in different cells, the individual cells acquire new identities and specialized functions.

Scientists had thought that fertilized eggs use the enzyme Tet to remove methyl groups from DNA. But today's results show that this is only half of the story. When the research team, from the MRC Clinical Sciences Centre (CSC) based at Imperial College London, genetically engineered mice so that their fertilized eggs lacked Tet3 (one of the Tet enzymes specifically present in the egg) they saw that the eggs could still remove the methyl groups. The same happened when they chemically blocked Tet's action. According to the scientists, this shows that Tet is not the only way in which fertilized eggs remove this modification on the DNA.

"What we've shown is that the Tet explanation is partly true, but it's not the complete story. We tried to dig a little deeper," says Rachel Amouroux who is the first author of the research. The study suggests that another, unknown mechanism is involved.

Understanding how these methyl group switches are removed could help scientists to produce immature cells, known as stem cells, in the laboratory. These cells are important because their ability to develop into any cell in the body means they can be used to repair or replace damaged and diseased tissue. Scientists make stem cells by 'reprogramming' mature cells, which turns back the clock so that the cells shift back into their immature state.

Scientists don't fully understand how this process happens naturally. If they can find out what's really happening here, they may be able to generate stem cells more efficiently.

Current techniques successfully reprogramme only a small proportion of cells. Even in those that are successfully reprogrammed there can be subtle but important variations that make them unsuitable for medical treatments.

The CSC scientists developed a new technique in order to follow the activity of Tet enzyme in the egg in greater detail than had been possible before. "This cutting edge technology uses mass spectroscopy, a method that breaks the DNA into single 'letters' then precisely analyses each of them and any chemical modifications of them," says Petra Hajkova, who leads the CSC's Reprogramming and Chromatin group, where the research was carried out.

"We found that the reprogramming process is much more complicated than previously thought," says Hajkova. "There is a constant race between the mechanisms removing the chemical modifications, and the mechanisms trying to put them back into place. When we want to reprogramme a cell, we have to think about both -- how to remove the modifications and, equally importantly, how to protect the newly unmodified DNA from becoming modified again."

Thwarting abnormal neural development with a new mutation

Researchers at the RIKEN Brain Science Institute in Japan have discovered how to reverse the abnormal axonal development characteristic of CFEOM3, a congenital disease that affects the muscles that control eye movements. Published in *Nature Communications*, the work shows how creating a specific mutation rescued abnormal axonal growth in the developing mouse brain.

During normal development of the nervous system, axons--the output end of neurons--must grow towards specific locations and make precise connections with other neurons. In CFEOM3, the nervous system governing eye movements does not develop properly because of defects in axon guidance that are associated with mutations in the protein β3-tubulin. Chains of tubulin molecules form microtubules that function in intracellular transport and structure, and β3-tubulin is a special type that is most abundant when axons are growing in the developing nervous system.

Some of the β3-tubulin mutations in CFEOM3 have been linked to microtubule interactions with kinesins--proteins that use energy to move from one end of a microtubule to the other.

"Our original aim was to understand the molecular mechanism underlying kinesin-tubulin interaction in the pathogenic mutants," explains lead author Itsushi Minoura. "Surprisingly, the kinesin mutants that we created effectively rescued kinesin motility and axonal growth, even in live mice."

The team began looking at the role of a specific amino acid location on β3-tubulin called R262, because the R262 mutation is the most common mutation in patients with CFEOM3. Using a recently developed baculovirus-insect cell-expression system, they first found that in vitro, this mutation does indeed inhibit the ability of kinesin--specifically the kinesin KIF5B-- to move along microtubules formed from β3-tubulin. In fact, the kinesin would not even bind to the mutant microtubules.

The team reasoned that if they knew what part of the kinesin interacted with the microtubule, they could then look for kinesins with mutations at that location, and perhaps find one that was able to move along the R262 mutant microtubules. The crystal structure of the kinesin-microtubule complex indicated that β3-tubulin binds to kinesin KIF5B at location D279. After several experiments, they found what they were looking for: replacing D279 with another amino acid--making a D279R mutant--allowed the kinesin to move along β3-tubulin microtubules with the R262 mutation.

Next, researchers tested whether they could use the D279R kinesin mutant to prevent abnormal axon growth in cultures neurons. They transfected the mutant β3-tubulin into dissociated embryonic neurons and as expected, saw significantly reduced axonal growth. They then found that neurons co-transfected with both mutants grew a normal length, and the abnormality was successfully suppressed.

After repeating the experiment with a mutant of another kinesin--D325R KIF2A--known to be important to the developing nervous system, researchers tested their theory in an in vivo experiment in the developing mouse brain. To do this, the disease-causing mutant tubulin and each disease-correcting mutant kinesin were transfected together into mouse embryos using in utero electroporation--a process that uses electric pulses to briefly open pores in cell membranes of embryos in uterus, allowing injected DNA to pass through. The team found that the both kinesin mutants suppressed abnormal axonal growth in the developing brain caused by the R262 microtubule mutation.

Notes Minoura, "while the rescue experiment is not available for humans, understanding the roles of the many types of tubulin in normal mammalian brain development is an important step towards understanding the pathogenesis of many neurodevelopmental disorders such as lissencephaly and polymicroglia."

Brothers-in-Arms: How a Tumor Suppressor Gene and Chromosome-Protecting Proteins Work Together to Stave Off Cancer

When it comes to genes associated with cancer, none have been studied more extensively than p53, a tumor suppressor gene that serves as the guardian of our genetic information. More than half of all cancers have mutations of p53, meaning that this particular gene must often be suppressed in order for a cancer to grow and spread.

P53 does not act alone in its protection of our genetic information. Telomeres – structures of proteins that cap off and protect our DNA at the tips of chromosomes like the aglets or clear tips of shoelaces – preserve these vital instructions as well. However, despite both p53 and telomeres offering similar benefits, the role of this key tumor suppressor gene as it relates to telomeres had never been properly described.

Now, new research from scientists at The Wistar Institute shows that p53 is able to suppress accumulated DNA damage at telomeres. This is the first time this particular function of p53 has ever been described and shows yet another benefit of this vital gene.

The gene p53 regulates our genome's integrity. When DNA is damaged by cellular stress or other means, p53 helps to activate the transcription of genes that help with controlling the cell cycle and inducing apoptosis, or cell death. However, prior studies have shown that p53 can bind at many locations across the genome, including many sites that are not responsible for activating these regulatory genes, and p53 itself has many distinct binding sites. Since both p53 and telomeres protect the genome, Wistar's team wanted to focus on these binding sites to see how the two might be more closely related than has ever been shown.

"We believed that p53 may be responsible for a more direct protective effect in telomeres," said Paul Lieberman, Ph.D., professor and program leader of the Gene Expression and Regulation program, director of the Center for Chemical Biology and Translational Medicine, and the Hilary Koprowski, M.D., Endowed Professor at The Wistar Institute, and lead author of the study.

Using ChIP-sequencing, which allows researchers to study interactions between proteins and DNA, a team of scientists at Wistar identified p53-binding sites in subtelomeres. These are segments of DNA situated in between telomeres and chromatin, the complex of DNA and proteins found in the nucleus of our cells.

The researchers found that when p53 was bound to subtelomeres, the protein was able to suppress the formation of a histone modification called gamma-H2AX. This histone is modified in greater amounts when there is a double strand break on DNA. If it persists, the break is not repaired, so suppressing its expression means that the DNA is being preserved. Additionally, p53 was able to prevent DNA degradation in telomeres, thereby keeping them intact and allowing them to more properly protect the tips of our chromosomes.

“Based on our findings, we propose that the modifications to chromatin made by p53 enhance local DNA repair or protection,” Lieberman said. “This would be yet another tumor suppressor function of p53, thus providing additional framework for just how important this gene is in protecting us from cancer.”

Gene therapy for rare bleeding disorder achieves proof-of-concept

Hematology researchers have used a single injection of gene therapy to correct a rare bleeding disorder, factor VII deficiency, in dogs. This success in large animals holds considerable potential for a safe, effective and long-lasting new treatment in humans with the same bleeding disorder.

"Our finding has great clinical relevance for patients with factor VII deficiency," said study leader Paris Margaritis, D. Phil., a hematology researcher at the Raymond G. Perelman Center for Cellular and Molecular Therapeutics (CCMT) at The Children's Hospital of Philadelphia (CHOP). "These dogs have the type of mutation found in the majority of patients with this disorder, so this approach could lead to a sustained gene therapy in people."

The Margaritis team collaborated with University of North Carolina (UNC) scientists, led by Tim Nichols, M.D., professor of Medicine and Pathology at the UNC School of Medicine.

Factor VII deficiency is rare, found in about one in 300,000 to one in 500,000 people. Because a gene mutation impairs normal production of a blood clotting factor, patients may suffer excessive bleeding in the central nervous system or GI tract, or after surgery or an injury. Female patients may suffer excessive menstrual bleeding.

Factor VII (FVII) deficiency has a range of severity, with about 40 percent of patients having severe disease. They are most commonly treated with regular infusions of clotting factor. Unlike hemophilia, a better-known bleeding disorder that predominantly affects males, factor VII deficiency strikes males and females equally.

Gene therapy proposed for bleeding disorders involves introducing DNA carrying the code to produce the specific clotting factor lacking in patients. Researchers at CHOP and elsewhere have bioengineered an adeno-associated virus (AAV), which does not cause disease, as a vector to deliver DNA into cells where it can express enough factor to make the blood clot normally. Over the past 15 years, CHOP hematology researchers have performed clinical trials of gene therapy for hemophilia B that have helped define efficacy and dosing levels in humans.

The CCMT at CHOP houses a clinical-grade laboratory that manufactures gene therapy vectors, including the AAV vectors used in the current study. Margaritis, a member of the CHOP group long engaged in hemophilia research, currently leads a laboratory focused on factor VII deficiency as well as hemophilia.

"We developed a unique animal model of this disease after identifying dogs with naturally occurring factor VII deficiency," said Margaritis. "Our investigations enabled us to design the corrective gene to insert into our virus vector in the current study."

The CHOP team collaborated with scientists at UNC who have a long-established colony of dogs for hematology research. Based on previous work by Margaritis, the UNC team identified dogs for this gene therapy study.

Nichols, the director of UNC's Francis Owens Blood Research Laboratory, characterized factor VII deficiency in four individual dogs. Using the AAV vectors supplied by Margaritis, Nichols injected the dogs with varying dosages and monitored their health outcomes and biological markers over several years.

The treated dogs had expressed levels of clotting factor VII that would be therapeutic in humans, with long-term stability. In one dog, the effects persisted nearly three years. Based on kidney function, liver function, and blood measurements in the dogs, the treatment was safe, and did not elicit unwanted immune responses.

The current study sets the stage for clinical trials in humans. This gene therapy may especially benefit young children with severe bleeding from factor VII deficiency, such as patients receiving care in CHOP's hematology program.

"This work is very exciting and promising," said Nichols, who added, "The FVII-deficient dogs tolerated the initial gene therapy infusions very well and have had no adverse side effects over several years of follow up. In other related studies in dogs with hemophilia B, similar positive findings have translated to people with hemophilia B." Both Nichols and Margaritis agreed: "The table is now set to propose clinical trials that would treat people who suffer from FVII deficiency."

How three genes you've never heard of may influence human fertility

Researchers, including Hart, have found that in each of these diverse organisms, natural selection is acting on genetic aspects of the fertilization process, making some pairs of individuals more likely to conceive than others.

Hart's interest in the genetics of reproduction has focused mostly on sea stars and sea urchins. As a zoologist and population geneticist, he wants to know: how does one species split into two?

In a recent project working on these unassuming invertebrates, Hart and his colleagues discovered an exciting new piece of this evolutionary puzzle: the fertility rate of mated sea stars depends on what forms of reproductive genes they have. In other words, male and female sea stars with certain types of genes might successfully produce offspring, whereas sea stars with other combinations of gene pairs fail to reproduce.

To Hart, this finding suggested that, over time, genetic incompatibility could cause populations of sea stars to gradually separate into different species. But it also had wider implications about fertility, and he wondered if researchers of fertilization biology and population genetics had found similar evidence of selection for certain combinations of genes in other study systems.

Indeed, in mice and in humans, researchers have been examining two kinds of genes: genes expressed in the mammalian egg coat -- which Hart describes as the "fibrous, sugary, sticky mass" that binds the sperm to the egg -- and genes expressed in the sperm, in order to understand how evolution may be proceeding in the genetic code.

In humans, Hart is working on three specific genes. ZP2 and ZP3 are egg coat genes, named for the zona pellucida, the technical term for the egg coat. Nearly all mammals have these genes, which make the proteins that interact to form the egg coat. C4BPA is responsible for producing a sperm protein that binds to the egg coat.

Back in 2010, Dr. Rori Rohlfs, who now works for the University of California, Berkeley, found that certain forms of the ZP3 gene occur alongside certain forms of the C4BPA gene more often than one would expect due to chance alone. Such associations between genes located on completely different chromosomes -- as ZP2, ZP3, and C4BPA are -- are rare in nature, and usually occur when the genes involved do something very important for the organism. From the perspective of evolutionary fitness, perhaps no function is more important than the ability to reproduce.

Fascinated by Rohlf's results, Hart and his colleagues set out to follow up on her work, temporarily leaving sea stars and sea urchins behind to delve into the human genome.

Their most recent findings -- which hint at something special about human evolution -- startled him.

The slow march towards species divergence is evolution's hallmark. Yet, Hart and his team's evidence points to just the opposite process in humans. "Human populations are not evolving to become reproductively isolated from each other," he says.

"There are some really important, highly conserved functions of those proteins," Hart says of the proteins encoded by ZP2 and ZP3. The absolute necessity of those proteins to an individual's ability to reproduce leads researchers to expect that most sites in the genes encoding those proteins will be relatively unchanged through generations, a phenomenon called negative selection.

"But there are a few that seem to be highly variable, and where the variation appears to be maintained by positive selection," he adds. "That's what we seem to have found."

Some of the most intriguing evidence in support of this idea has come from paleogeneticists. These scientists, who study ancient human genomes, have identified exactly the same genetic variants from modern humans in the genetic data of Neanderthals and Denisovans, human lineages that migrated out of Africa hundreds of thousands to a million years ago.

The consistency of these specific genes through much of human history connects Hart's work to the broad, interwoven story of evolution -- from invertebrates to vertebrates -- in unexpected ways.

In his work on sea stars and sea urchins, Hart did not have cause to reflect on the discrepancy between how individuals choose a mate and whether they can reproduce successfully. "In a lot of marine animals that spawn sperm and eggs into the plankton, the adult organisms never really 'meet' each other," he says. "Instead, mate selection, to the extent that it happens, happens at the level of these kinds of biochemical interactions between sperm and eggs."

"Now, we don't really think about mammalian mate selection happening that way," he adds, pointing out that human 'mates' are usually chosen through behavioral interactions, be they in the office or at the bar. "So it's sort of surprising to find this molecular signature of selection acting on these genes that seem most likely to affect the fitness of individuals."

In this way, Hart's current research prompts us to reflect on how natural selection operates in the evolution of the human species -- perhaps as much at the level of invisible molecules as at the level of attributes we can see.

Age-old mystery of why cells use fermentation unraveled

Wine, beer and yogurt are produced when microorganisms convert sugar into alcohol, gases or acids. But this process of fermentation--which is used by bacteria, fungi and other fast-growing cells to generate energy in the absence of oxygen--is a much less efficient way of generating energy for cells than aerobic respiration.

So why do many organisms use this seemingly wasteful strategy to generate energy instead of aerobic respiration, even when oxygen is readily available?

Biologists have pondered this conundrum for nearly a century and dubbed it the "Warburg effect" after the Nobel-Prize winning cell biologist Otto Warburg. He discovered in the 1920s that cancer cells generate energy by fermenting glucose, which generates a great deal of metabolic waste such as lactic acid.

Heavy usage of glucose by fermentation is, in fact, how tumors are identified in PET scans. But if this process is so inefficient, Warburg and others wondered, why do so many organisms depend on it instead of using the more efficient process of aerobic respiration?

A team of physicists and biologists from UC San Diego may have finally found the answer to this nearly 100-year-old mystery. In this week's issue of the journal *Nature*, the researchers examined the metabolic costs of synthesizing the enzymes and other biological apparatus required for fermentation and aerobic respiration within the bacterium E. coli as well as the metabolic savings of generating energy through aerobic respiration. They found that the cost of protein synthesis overrules the metabolic savings for fast growing cells.

"What we discovered could be compared to the difference between generating energy by a coal factory versus a nuclear power plant," said Terry Hwa, a professor of physics and biology at UC San Diego who headed the study. "Coal factories produce energy less efficiently than nuclear power plants on a per-carbon basis, but they are a lot cheaper to build. So the decision of which route to generate energy depends on the availability of coal and the available budget for building power plants."

"For cells, it turns out that there are also two costs to consider," he added. "One is the cost of raw material. Aerobic respiration generates more energy per carbon atom than fermentation. The other is the opportunity cost of synthesizing enzymes. This cost refers to the number of the protein-making machinery, or ribosomes, that need to be recruited to synthesize the relevant enzymes. We showed that the enzymes for respiration are bulky and slow compared to those for fermentation, so a lot of such enzymes need to be synthesized, tying up a lot of ribosomes, in order for respiration to happen at substantial rates. This is an important cost because the number of ribosomes is the growth limiting factor."

"For fast growing cells with plenty of nutrients, if a lot of ribosomes are used to make respiratory enzymes, then few of them are available to make other growth proteins, including

the ribosomes themselves. This would slow down growth and is disadvantageous to cells. The higher carbon efficiency of respiration is not an important consideration here since nutrients are plentiful. On the other hand, when nutrients are scarce and cells cannot grow fast, then the demand for ribosomes by other cellular functions is reduced, and the cost of tying up ribosomes is less important. In the meantime, using respiration to generate energy conserves the precious carbon supplies, which is a much more important consideration in poor nutrient conditions."

"Of these two costs the cell needs to consider when generating energy, the cost of carbon is universally recognized, that is, respiration is more carbon-efficient. What we established in this study is that the cost of making the energy-generating apparatus is also substantial, and is in fact the dominant cost for fast growing cells."

The idea of this opportunity cost to cell growth was first suggested several years ago by a team of theoretical biologists from the Netherlands. In the UC San Diego study, Hwa and his collaborators experimentally characterized the cost of synthesizing fermentation versus respiratory enzymes by using proteomic mass spectrometry and discovered that respiratory proteins are twice as expensive as fermentation proteins for the same rate of energy generation. Their study is the first time such a cost has been established for any living system. The researchers also developed a mathematical model that quantitatively predicted the pattern of metabolic waste excretion in response to perturbations they applied to affect the physiological state of growing cells.

While it is not clear whether the same rationale underlies the origin of "wasteful metabolism" in cancer, the researchers said, they believe their results provide another way to think about the process.

"Instead of something going wrong that should be fixed, this may be the universal strategy necessary for rapidly growing cells," explained Hwa. "The results may also have implications in biotechnology: metabolic engineers are always trying to reduce metabolic waste in engineered organisms in order to reduce cost. Our findings suggest that reducing waste may be detrimental to the organisms and different strategies need to be devised to increase metabolic efficiency."

Another milestone in hybrid artificial photosynthesis

A team of researchers at the U.S. Department of Energy (DOE)'s Lawrence Berkeley National Laboratory (Berkeley Lab) developing a bioinorganic hybrid approach to artificial photosynthesis have achieved another milestone. Having generated quite a buzz with their hybrid system of semiconducting nanowires and bacteria that used electrons to synthesize carbon dioxide into acetate, the team has now developed a hybrid system that produces renewable molecular hydrogen and uses it to synthesize carbon dioxide into methane, the primary constituent of natural gas.

"This study represents another key breakthrough in solar-to-chemical energy conversion efficiency and artificial photosynthesis," says Peidong Yang, a chemist with Berkeley Lab's Materials Sciences Division and one of the leaders of this study. "By generating renewable hydrogen and feeding it to microbes for the production of methane, we can now expect an electrical-to-chemical efficiency of better than 50 percent and a solar-to-chemical energy conversion efficiency of 10-percent if our system is coupled with state-of-art solar panel and electrolyzer."

Yang, who also holds appointments with UC Berkeley and the Kavli Energy NanoScience Institute (Kavli-ENSI) at Berkeley, is one of three corresponding authors of a paper describing this research in the *Proceedings of the National Academy of Sciences (PNAS).* The paper is titled "A hybrid bioinorganic approach to solar-to-chemical conversion." The other corresponding authors are Michelle Chang and Christopher Chang. Both also hold joint appointments with Berkeley Lab and UC Berkeley. In addition, Chris Chang is a Howard Hughes Medical Institute (HHMI) investigator.

Photosynthesis is the process by which nature harvests the energy in sunlight and uses it to synthesize carbohydrates from carbon dioxide and water. Carbohyrates are biomolecules that store the chemical energy used by living cells. In the original hybrid artificial photosynthesis system developed by the Berkeley Lab team, an array of silicon and titanium oxide nanowires collected solar energy and delivered electrons to microbes which used them to reduce carbon dioxide into a variety of value-added chemical products. In the new system, solar energy is used to split the water molecule into molecular oxygen and hydrogen. The hydrogen is then transported to microbes that use it to reduce carbon dioxide into one specific chemical product, methane.

"In our latest work, we've demonstrated two key advances," says Chris Chang. "First, our use of renewable hydrogen for carbon dioxide fixation opens up the possibility of using hydrogen that comes from any sustainable energy source, including wind, hydrothermal and nuclear. Second, having demonstrated one promising organism for using renewable hydrogen, we can now, through synthetic biology, expand to other organisms and other value-added chemical products."

The concept in the two studies is essentially the same -- a membrane of semiconductor nanowires that can harness solar energy is populated with bacterium that can feed off this energy and use it to produce a targeted carbon-based chemical. In the new study, the membrane consisted of indium phosphide photocathodes and titanium dioxide photoanodes. Whereas in the first study, the team worked with *Sporomusa ovata,* an anaerobic bacterium that readily accepts electrons from the surrounding environment to reduce carbon dioxide, in the new study the team populated the membrane with*Methanosarcina barkeri*, an anaerobic archaeon that reduces carbon dioxide using hydrogen rather than electrons.

"Using hydrogen as the energy carrier rather than electrons makes for a much more efficient process as molecular hydrogen, through its chemical bonds, has a much higher density for storing and transporting energy," says Michelle Chang.

In the newest membrane reported by the Berkeley team, solar energy is absorbed and used to generate hydrogen from water via the hydrogen evolution reaction (HER). The HER is catalyzed by earth-abundant nickel sulfide nanoparticles that operate effectively under biologically compatible conditions. Hydrogen produced in the HER is directly utilized by the*Methanosarcina barkeri* archaeons in the membrane to produce methane.

"We selected methane as an initial target owing to the ease of product separation, the potential for integration into existing infrastructures for the delivery and use of natural gas, and the fact that direct conversion of carbon dioxide to methane with synthetic catalysts has proven to be a formidable challenge," says Chris Chang. "Since we still get the majority of our methane from natural gas, a fossil fuel, often from fracking, the ability to generate methane from a renewable hydrogen source is another important advance."

Adds Yang, "While we were inspired by the process of natural photosynthesis and continue to learn from it, by adding nanotechnology to help improve the efficiency of natural systems we are showing that sometimes we can do even better than nature."

In addition to the corresponding authors, other co-authors of the *PNAS* paper describing this research were Eva Nichols, Joseph Gallagher, Chong Liu, Yude Su, Joaquin Resasco, Yi Yu and Yujie Sung.