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Optogenetics: switching cell activity on and off with light

What still sounds like science fiction to the general public, has long been within reach: for many years, scientists have been able to manipulate neural activity selectively with light. They use different wavelengths to turn cells on and off, as if they were a standard switch. Optogenetics is an emerging technology that combines optics and genetics. The technology is already used in many different ways for many different purposes by numerous research laboratories around the world. It is also fuelling hopes that one day it may be possible to cure neurological disorders such as epilepsy. Recent developments show that optogenetics can do even more: in the future, it will be possible to control all signalling processes in cells, including gene expression, with light.

Light-gated ion channels were discovered in Chlamydomonas algae.
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Back in 1999, Francis Crick first proposed the idea of using light to control neural activity. Did he really know that this would work? Most likely. Around 15 years later, optogenetics has become a versatile and powerful technology for research laboratories around the world. In 2010, the scientific journal "Nature Methods" named optogenetics as "method of the year", thus fuelling the hope of neuroscientists that the technology will help them to represent the neural network in real time and to better understand its activities.

Optogenetics combines genetics and optics to control the electrical activity of genetically modified cells by shining light on them. The earliest optogenetic approaches go back to 2002, when scientists discovered a light-dependent ion channel in Chlamydomonas reinhardtii green algae. These unicellullular phototactic algae have two flagellae with which they can move towards a light source.

Chlamydomonas paves the way to optogenetics

The algal membrane contains a light-sensitive molecule that forms a transmembrane channel. The channel opens in response to illumination with blue light, resulting in an influx of calcium ions and depolarisation of the membrane. Calcium ions that enter the cells induce flagellar movement and the algae start to move towards light. The blue light-sensitive algal molecules were named channelrhodopsin 2 (CHR2).

The archaebacterium Natronomonas pharaonis (NpHR) possesses a halorhodopsin, a yellow light-activated ion pump that transports negatively charged chloride ions across the plasma membrane into the cell, resulting in the hyperpolarisation of the membrane.

The two rhodopsins can be transferred to and expressed in eukaryotic cells in order to confer light sensitivity onto cells that are normally unresponsive to light (e.g. neurons). The two channels have an antagonistic effect when expressed in the same neuron. Illumination with blue or yellow light enables the specific control of the ion channels and induction of cellular processes at defined points in time, and hence the optical activation (channelrhodopsin 2) and silencing (halorhodopsin) of neural activity with millisecond precision.

Bioengineering of signalling pathways and gene expression

The latest developments in the field of optogenetics suggest that we have already arrived in the future. Researchers are now able to couple photoreceptors such as plant phytochrome B or fungal Vivid to proteins that are important checkpoints in cellular signalling pathways. The coupling of kinases with plant-derived photoreceptors enables researchers to control the activity of the proteins by exposing them to light of a particular wavelength. The combination of a phytochrome molecule with a specific promoter enables researchers to switch relevant genes on or off with red or far-red light; only activated genes are transcribed and translated into a protein. The researchers have precise control over where and when they want a particular gene to be expressed.

Brain Prize for optogenetics pioneers

An international team of biophycisists, neurophysiologists and botanists were awarded the Grete Lundbeck European Brain Research Foundation's Brain Prize in May 2013 for their achievements in the field of optogenetics. The researchers, who transferred the algal rhodopsin gene to egg cells of the African frog Xenopus laevis, were able to show that the algal rhodopsin molecule combines light receptor and ion channel in one protein.

In 2003, a group of researchers successfully expressed for the first time a channelrhodopsin variant in the surface membrane of mammalian cells, thus giving researchers around the world the ability to activate cells quickly and reliably with light. This is done as follows: the gene of a light-sensitive channel protein is removed from microorganisms – green algae or archaebacteria – and transferred into the genome of a mouse embryo, for example. It is only inserted into DNA sections that are exclusively expressed in certain cell types, e.g. dopaminergic neurons. Subsequently, only dopamine-releasing neurons will become responsive to light.

A plethora of applications

The method enables the selective extracellular control of specific cells with light: cells that do not contain light-sensitive channel proteins do not respond when exposed to light. The advantage of the method is that it is more accurate than extracellular electrostimulation and quicker than drugs. The method is particularly useful for researchers who require a very tight (in the millisecond range) and reversible control over the activity pattern of the neurons that express these channel proteins.

Optogenetics facilitates biomedical research into brain function and dysfunction and is currently being tested for its suitability for investigating Parkinson's disease and epilepsy brains in animal models. This method enables scientists to modulate specific cell populations in a spatially restricted manner. Optogenetics differs from electrical stimulation in that the latter is the simultaneous excitation of large radial areas with no differentiation between different cell types. The use of optogenetic methods is also highly promising in the field of cell biology where scientists can use the tools to manipulate signalling cascades and other intracellular processes in order to obtain a greater understanding of the underlying mechanisms.

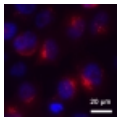
The questions as to whether it is possible to treat diseased neurons in the human brain and whether optogenetics can or should be used for developing light-modulated drugs must be examined critically. However, whatever answer researchers come up with, the light-sensitive molecules must be used very selectively and only target specific ion channels in specific cell types. It can be safely assumed that the application of optogenetics for transducing signals and regulating genes will dramatically expand biotechnological and biomedical research and application potential within the next few years. The current dossier introduces and provides initial insights into the topic.

Stephanie Heyl - 13th January 2014
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