Optogenetics 3.0

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Mechanism aside, the main point to appreciate is that the association of p120 with cadherin is truly the limiting factor that determines whether a given cadherin molecule will persist on the cell surface or will be targeted for destruction. We know that cadherins are internalized by endocytosis when p120 dissociates from the juxtamembrane domain of cadherin (Figure 1) and that factors like clathrin and ubiquitin ligase Hakai are likely players in the demise of p120-deprived cadherins (Davis et al., 2003; Xiao et al., 2003). We also know that α- and β-catenins are essentially irrelevant because they stay attached to cadherins and thus are internalized simultaneously.

What we don’t know is how these events unfold under normal circumstances in the cell. Presumably, the biophysical characteristics identified by Ishiyama et al. (2010) and described above do not alone drive cadherin turnover. If other mechanisms contribute, what might they look like? The simplest mechanism is shown in Figure 1 (right panel). In this model, p120 is modified, most likely by a kinase, in response to specific signals. Such a kinase could phosphorylate p120, the cadherin juxtamembrane domain, or both, resulting in separation of p120 from the complex and subsequent internalization of cadherin. A second model (not shown) supposes that the role of p120 is to recruit an additional factor to the cadherin complex, whose presence is required for cadherin retention and stability at the cell surface. In this scenario, the absence of p120 leads to the loss of the stability factor, and the hapless cadherin is sacrificed due to lack of support. Both of these mechanisms might be tuned up or down as needed, but the relevant players have not been clearly identified.

The first visualization of p120’s molecular makeup and its interaction with the cadherin juxtamembrane domain (Ishiyama et al., 2010) likely marks the beginning of a new generation of experiments that will take advantage of these exquisite molecular insights. Minimally, the structure will lead to increasingly elegant reagents for selectively uncoupling distinct functions of p120 and improved interpretation of experimental results. However, given that the p120/cadherin interaction controls almost all of the classical cadherins and that p120 is frequently downregulated in most of the major cancers, the results presented by Ishimaya et al. (2010) will probably have far-reaching consequences.

REFERENCES

Optogenetics 3.0

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Optogenetic methods use light to modulate the activities of target cells in vivo. By improving inter- and intracellular trafficking of light-sensitive switch proteins called opsins, Gradinaru et al. (2010) have developed a new generation of optogenetic tools capable of regulating the activity of targeted neurons with exquisite precision and efficiency.

Switching a well-defined cell population on and off at will is a desirable goal for systems biology research. Scientists have developed various methods across different species to target specific cells and make them controllable by diverse external factors such as temperature and chemicals (Alexander et al., 2009; Liu and Davis, 2006). However, when it comes to temporal precision, literally nothing beats the speed of light. The successful marriage of optical technologies with molecular genetics has resulted in the new kid on the techniques block: optogenetics. Optogenetics is a rapidly developing technique that is being used by neuroscientists to manipulate the activity of selected neuronal populations.
Figure 1. Targeting Specific Neurons by Optogenetics

Neurons A and B are neighboring neurons of the same type, with axonal projections ending in different brain regions containing neurons C and D, respectively. A virus encoding a WGA-CRE fusion protein is taken up by the soma of neuron C and the fusion protein product WGA-CRE trans-synaptically traffics into neuron A. Another virus coding for a CRE-dependent light-activated opsin effector was taken up by both neurons A and B because of their close spatial proximity. Only in neuron A, in the presence of WGA-CRE, is the construct processed and the final light-sensitive protein product (ChR2 or NpHR) made. Thus, neuron A is specifically labeled and can be distinguished from neuron B on excitation with the correct wavelength of light. Such optogenetic approaches can be used to manipulate the activity of a single neuron in a cell population in living animals with great precision.
molecular genetics is underdeveloped, such as primates, this is almost out of the question. Even for organisms with a good collection of transcriptional promoters, such as mice and fruit flies, targeting a subpopulation of cells within a genetically and anatomically “homogeneous” cell population is a challenge. To address these issues, the authors resorted to trans-synaptic trafficking. They used two viruses: one encoding CRE recombinase fused to the transcellular tracer protein wheat germ agglutinin (WGA) and a second encoding a CRE-dependent opsin. They delivered these two viruses to a pair of remote but anatomically connected brain regions in rats or mice, one virus each to one of the two regions, and successfully labeled and optically controlled the subpopulation of neurons with projections connecting these two brain regions (Figure 1). This approach also raises an intriguing possibility that activation or inhibition may be targeted to specific axonal branches, rather than to the neuronal soma (cell body), potentially increasing the precision of optogenetic manipulation. Overall, trans-synaptic labeling of anatomically connected neurons with a WGA-CRE fusion protein enabled targeting of specific neurons on the basis of their synaptic connection patterns, thus opening new doors for the precise manipulation of neural circuits.

These optogenetic techniques described by Deisseroth and his team, as well as by others, provide powerful new tools for neuroscience research. Although these methods based on light-gated ion channels are effective only in cells (neurons, muscle, endocrine cells, etc.) that can be rendered excitable by these channels, some additional recent developments promise broadening of the range of target cell types that can be manipulated by optogenetics. For example, new light-sensitive G protein-coupled receptors (dubbed optoXRs) have the potential to influence signaling cascades in cell types other than neurons (Airan et al., 2009). Theoretically, light-gated calcium ion channels could also be useful, as calcium ions are a universal secondary messenger in all known cell types. Expanding optogenetic tools so that they can be applied more broadly is the goal of optogenetics 3.0 and beyond.

REFERENCES


Time for Bacteria to Slow down

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The speed of the bacterial flagellar motor is thought to be regulated by structural changes in the motor. Two new studies, Boehm et al. (2010) in this issue and Paul et al. (2010) in Molecular Cell, now show that cyclic di-GMP also regulates flagellar motor speed through interactions between the cyclic di-GMP binding protein YcgR and the motor proteins.

Cyclic di-GMP is the molecule of the moment in bacteriology. This ubiquitous secondary messenger has been implicated in myriad processes from pathogenicity to synthesis of pili (hairlike appendages involved in biofilm production) (reviewed in Hengge, 2009). Now two new papers, one in this issue of Cell (Boehm et al., 2010) and one in the upcoming issue of Molecular Cell (Paul et al., 2010), reveal the direct involvement of cyclic di-GMP in the regulation of flagellar movement and bacterial swimming. Cyclic di-GMP is synthesized from two molecules of GTP by diguanylate cyclase domains and is broken down by phosphodiesterase domains. The