Light Up the COVID-19

Introduction

Transmissible disease or infectious disease is distinguished as disorders happened by pathogenic microorganisms. Chemical monitoring of cellular pathways of host cells or pathogens has some limitations such as diffusion and polytrophic effect. Furthermore, chemical methods to control pathogens have unintentional effects on other pathways that make difficult information analysis. Optogenetics has solved these issues by the introduction of light controllable molecules that can manipulate molecular interactions, gene expression, and signal transduction cascade with high accuracy and efficiency.[1-3]

After the Spanish influenza pandemic over a century ago, at the beginning of 2020, the universe unexpectedly faced a new coronavirus prevalence that is still running across borders and has the capacity to become a long-term global health issue. Extensive attempts are on-going for vaccine and other treatment developments. Among the many directions of engaging coronavirus, optogenetics may respond to questions regarding mechanisms of coronavirus-host cell interactions.

The pioneering work of expression of light controllable adenylate cyclase in Toxoplasma gondii in 2013 opened new windows of opportunity to exploit optogenetics in control of host-cell interconnections.[4] Furthermore, by using gene-encoded Ca^{2+} indicator in *Toxoplasma gondii* and *Plasmodium falciparum*, monitoring and detecting calcium homeostasis has become possible.[5,6] These studies provided the basis for further applications of optogenetics in the understanding mechanisms of pathogenesis and subsequently antiviral therapy. In this article, we explain how we can benefit from the optogenetic tools to understand the virus-host interactions.

Optogenetic toolbox

Initially, optogenetics was included photo-switching proteins which can alter membrane potential or allow modulate intracellular pathways and molecular interactions. The development of gene-encoded light-activated sensors would be more useful to measure intracellular metabolites or messengers. Based on Addgene Database, more than 40 classes of optogenetic actuators and about 30 biosensors are available through Addgene. Most of these actuators have been generated for the study of neuroscience. Gradually, these tools developed and provide sparks to the other research area fields such as differentiation in parasites. Currently, it seems that this technology is ready to decipher some important questions in infection biology. Herein we highlight opto-tools for possible application of optogenetics in infection research and identify opportunities that this approach provides in viral infections such as COVID-19 pandemic.

Opsin

Targeting gradient ion homeostasis is critical during virus infection cycles. Norris *et al*. with screening over 2,000 drugs with novel anti-respiratory syncytial virus activity, found out the intracellular Na^+ and K^+ gradient is very important in virus replication cycle, especially in the first 4 h of infection and suggests a new antiviral strategy against the respiratory syncytial virus.[7] Channelrhodopsin-2 (ChR2) is a directly light-switched cation-membrane channel that is a main optogenetic toolbox.[8] Disturbance of ion composition by ChR in virus or host infected cells is a possible application of optogenetics to investigate virus-host interaction. Furthermore, optogenetics might help to shed light on monitoring ion hemostasis during viroporins which has a critical role in viral replication and pathogenesis.

Viroporins are small hydrophobic multifunctional proteins, virus-encoded membrane channels that operate as size-limited pores and ion-conducting channels and play a significant role in the viral particle assembly in all types of viruses including coronavirus envelope proteins.[9,10] Recently, Zabelskii *et al*. present two viral rhodopsin groups 1 OLPVR1 and VirChR1, from phycodnaviruses belonging to the nucleocytoplasmic large DNA viruses, which is highly selective to Na^+/K^+ gradient. However, the exact functions of these viral rhodopsins have not been established but could become useful instruments in virus reproduction studies.[11]

Genetically encoded calcium indicators

Ca^{2+} ions act as a multi-functional second messenger and play a fundamental role in the control of cell physiology such as proliferation, differentiation, transcription, contraction, secretion, and apoptosis. Thus, Ca^{2+} monitoring, not only in living cells but also in living organisms is critical to the study of various intracellular calcium signals. Genetically encoded calcium ion (Ca^{2+}) indicators are beneficial tools to record (Ca^{2+}) in determining cells and compartments.

Existing proof proposes that Ca^{2+} is required for coronavirus entry and replication. Recently, several investigations have shown that calcium channel blockers such as nifedipine and amlodipine can alleviate the mortality rate of COVID-19.[12] Furthermore, low levels of serum calcium have been demonstrated to be positively related to the acuteness of COVID-19. Moreover, Ca^{2+} ions are the central

key in coronavirus replication.[12] Therefore, manipulation of Ca^{2+} metabolism in virus infected host cells may provide new sights into the severity and treatment of COVID-19.

Photo-activated G protein-coupled receptors, receptor tyrosine kinases, G cyclic adenosine monophosphate (CaMP) 1-6, photoactivatable Ca^{2+} releaser, are optogenetics toolboxes which serve as a light-oscillator of Ca^{2+} that could be applicable to illustrate new perspective of Ca^{2+} metabolism in antiviral therapy.[13]

Cyclic nucleotide cyclase and phosphodiesterase

Cyclic nucleotide such as cyclic guanosine monophosphate (cGMP) and cAMP are important second messengers and has been identified to play crucial roles in many signaling pathways. Phosphodiesterase by hydrolyzing and nucleotide cyclase by synthesizing raised and reduced the level of cyclic nucleotides, respectively.[14] The level of intracellular cGMP and cAMP is associated with virus replication and pathogenesis. Recently, it has been shown phosphodiesterase could appear as a novel potential targeting COVID-19 treatment.[15] Previously, phosphodiesterase inhibitors have been used in the management of disorders such as fibrosis, inflammation, and thrombosis that show clinical symptoms that are entirely or partially similar to coronavirus signs.[15] These symptom similarities with COVID-19 support the assumption which phosphodiesterase inhibitors could be effective against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Moreover, light-dependent cyclic nucleotide cyclase and phosphodiesterase have the potential to clarify the mechanism underlying cNMP signaling and phosphoproteomic analysis to recognize the main signaling moderators.

Light-oxygen-voltage sensing domain 2-ornithine decarboxylase/B-LID degron

Regulation of protein stability and degradation in cells is a critical tool for studying protein function. Current methods mark proteins posttranslationally by ubiquitin, small molecules, or by fusing degradation motif (degrons). Optogenetics offers a novel photosensitive degradation motif which is degraded upon blue light illumination. Fusion proteins including this motif are quickly degraded in cells through blue light stimulation.[16] The light-oxygen-voltage sensing domain 2-ornithine decarboxylase/B-LID degron systems have been described which is very useful in the study of protein diminution rate, protein redundancy at light-fluxes. In addition, photo-activated CRISPR–Cas9 effector (LACE) technology was employed to control of protein function.[17]

Regulation of protein stability helped to illuminate the mechanisms underlying the virus entry, survival in the host cell, or transcytosis. For example, the study of binding stability of SARS-CoV-2 spike glycoprotein and angiotensin-converting enzyme2 during entry, optogenetics toolboxes not only can be useful for the comprehension of basic nature of virus but also support the advancement of vaccines and therapeutic drugs. The mentioned tools can be introduced in infected host to investigate the effect of host environment on virus. These tools also allow the change of epigenetic conditions, activation, or suppression of proteins in parasite or host cell.

Cryptochrome 2/ N-terminus of calcium and integrin-binding protein 1

The cryptochrome 2 (CRY2), light sensitive plant photoreceptors has become a strong and potent optogenetic instrument that permits light-controllable manipulation of different cellular pathways and signaling events in cells with sub-cellular spatial precision and sub-second time precision.[18] Kennedy *et al.* demonstrated that conformational changes in CRY2 induced by blue light stimulation and heterodimerization with its partner CIB1.[19] By fusion of CRY2/CIB1 with Cre recombinase system, the deletion of virulence factors and subsequently low pathogenicity of COVID-19 will be feasible.[20] Furthermore, the use of CRY2-CIBN/Rho GTPase fusion construct also enables the control of actin filament polymerization and relocation of infected-cell compartments[21] that might be beneficial in the study of coronavirus entry into human cells, cellular trafficking pathways relevant to viral entry, and host organelle infected by coronavirus.

Conclusions

Monitoring and tracing of virus tracts without influencing infected cell are almost infeasible with fluorophores and chemical modifiers. Conversely, high spatio-temporal control of host cells is encouraging. However, optogenetics does not yet common but suggests useful tools to manipulate and control biochemical processes in the pathogen and infected cell. The progress of optogenetics shall solve main problems with old methods in the way of recognition of host-pathogen interactions. Since the causes for pathogenesis of coronavirus and its complications are poorly understood, it is necessary to recognize signaling pathways in virus-host cell-infected interconnections and characterize their activity, which may finally lead to new drug targets.

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Conflicts of interest

There are no conflicts of interest.

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