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OPTICS: An interactive online platform for photosensory and bio-functional proteins in optogenetic systems

A B S T R A C T

High-precise modulation of bio-functional proteins related to signaling is crucial in life sciences and human health. The cutting-edge technology of optogenetics, which combines optical method with genetically encoded protein expression, pioneered new pathways for the control of cellular bio-functional proteins (CPs) using optogenetic tools (OTs) in spatial and temporal. Over the past decade, hundreds of optogenetic systems (OSs) have been developed for various applications from living cells to freely moving organisms. However, no database has been constructed to comprehensively provide the valuable information of OSs yet. In this work, a new database named OPTICS (an interactive online platform for photosensory and bio-functional proteins in optogenetic systems) is introduced. Our OPTICS is unique in (i) systematically describing diverse OSs from the perspective of photoreceptor-based classification and mechanism of action, (ii) featuring the detailed biophysical properties and functional data of OSs, (iii) providing the interaction between OT and CP for each OS referring to distinct applications in research, diagnosis, and therapy, and (iv) enabling a light response property-based search against all OSs in the database. Since the information on OSs is essential for rapid and predictable design of optogenetic controls, the comprehensive data provided in OPTICS lay a solid foundation for the future development of novel OSs. OPTICS is freely accessible without login requirement at https://idrblab.org/optics/.

1. Introduction

Photoreceptors including opsins, phytochromes, flavin-binding proteins, etc. have been identified in a wide range of species from microbe and plant to animal [1]. These photosensory proteins provide the living things with unique abilities to sense and respond to different types of light (Fig. 1A). By combing the methods of optical control and genetically encoded protein expression [2], the use of opsins for the first time to control neurons with light in 2005 indicates the emergence of "optogenetics" [3]. As a cutting-edge technology, diverse optogenetic systems (OSs) have been growing rapidly since then which completely revolutionized neuroscience, immunotherapy, and beyond [4].

In general, an OS comprises two main modules (Fig. 1B): the optogenetic tool (OT) [5]and the controlled protein (CP, also known as the cellular bio-functional protein) [6]. The OT, consisting of a photoreceptor, a cofactor, and (or) a complementary protein/partner, is regarded as the critical module of an OS [7]. Based on the distinct characteristics of OTs and CPs in terms of structure and function [8], current OSs can be classified into two conceptually different design types: including intermolecular proximity and intramolecular conformation changes [9]. In addition, an OS can be categorized into single-, dual-, and multiple-component systems according to the architecture of OT [10].

Over the last two decades, the repertoire of OTs has been largely enriched [11], which is benefited from the refinement of the sequence-structure-function relationships of photoreceptors [12]and their partners [13]. Meanwhile, the CPs related to various signaling pathways (e.g. mTOR [14], CRISPR/Cas [15], and $G_{i/o}$) and molecular functions (e.g. gene expression [16], subcellular localization [17], cellular decision-making [18], and tissue morphogenesis [19]) have been successfully incorporated into different OSs [20]. This integration enables precise modulation of signaling from living cells to freely moving organisms [21–23]. Therefore, the available data of current known OSs has attracted broad interests of scientists worldwide [24], spurring the rapid development of novel ones with the aid of artificial intelligence techniques including machining learning [25] and deep learning [26].

So far, several databases related to optogenetics (i.e. OptoBase [27], FPbase [28], and FBDB [29]) have been constructed and are currently active. However, no database has yet been developed to systematically provide up-to-date data on hundreds of OSs along with the vital information that is critical to precise control of various signaling pathways and molecular functions in both space and time. Therefore, a new interactive online platform for photosensory and bio-functional proteins in optogenetic systems is urgently needed. Here, a new interactive online platform for photosensory and bio-functional proteins in optogenetic systems (OPTICS) was therefore introduced.

2. Results and discussion

2.1. OSs Classification & mechanism of action

OSs in OPTICS are classified into nine classes (Fig. 2) based on the OT (photoreceptor) module [30]. Among them, cryptochromes (CRY2) and phytochromes (PHY)-based OSs mainly regulate protein function by spatially bringing fusion protein and recruited protein together through photoreceptor-partner heterodimerization upon illumination [31]. While fluorescent protein (e.g. dronpa) and cobalamin binding domain (CBD)-based OSs dissociate upon illumination, thereby relieving fusion protein to modulate the corresponding cellular signals [32]. UV receptor-based OSs regulate cellular signaling through photoreceptor monomerization and then photoreceptor-partner heterodimerization under ultraviolet light [33]. Opsin-based OSs, which are ion channel proteins located in the cell membrane, open in response to specific

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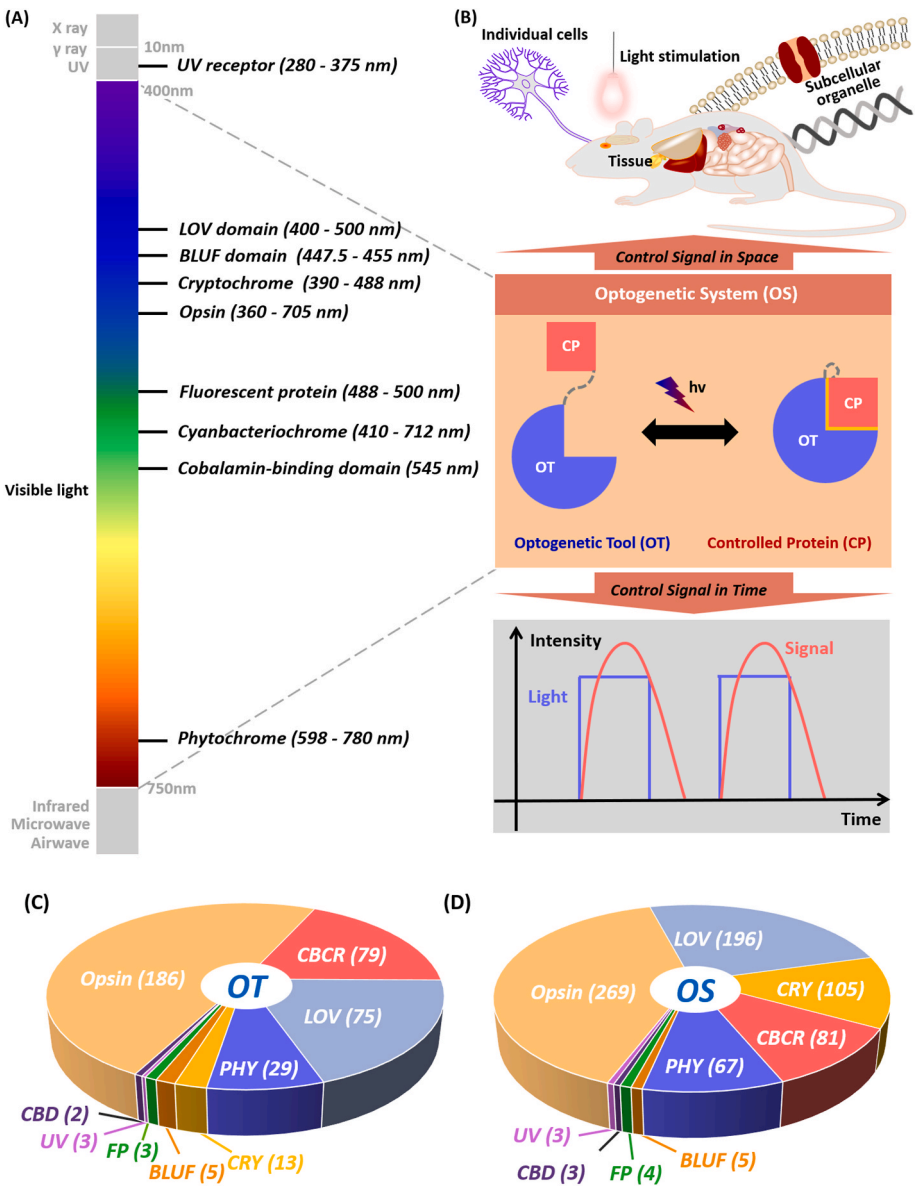

Fig. 1. A brief introduction of photoreceptors and optogenetic systems (OSs). (A) Protein classification, activation wavelengths, and the number of currently known photoreceptors. (B) Schematic diagram of OSs controlling cellular signals in space and time. In general, an OS comprises two main modules: the optogenetic tool (OT) and the controlled protein (CP, also known as cellular function protein). The statistics of (C) OTs and (D) OSs amount based on the classification of photoreceptors. The statistics defines a one to many relationship between OTs and OSs. LOV, CBCR, PHY, CRY, BLUF, FP, UV, and CBD are the abbreviations for photoreceptors light-oxygen-voltage domain, cyanobacteriochromes, phytochromes, crytochromes, blue light sesor using flavin, florescent protein, UV receptor, and cobalamin binding domain, respectively.

wavelengths of light, allowing ions to flow across membrane and directly affect cellular signals [34]. As for LOV domain-based OSs, a conserved C-terminal helix (Jα) remains folded in the dark which but unfolds upon illumination, thereby releasing the functional protein [35]. BLUF domain and cyanobacteriochromes (CBCRs)-based OSs mainly regulate functional proteins to produce signaling molecules such as cAMP through intramolecular conformational changes [36]. Therefore, according to the mechanism of action, OSs in OPTICS can be broadly divided into two main groups: light inducible dimerization and conformational change [2]. Besides, OSs can be categorized into single-, dual-, and multiple-component systems [34] based on the architecture of OT (photosensory domain and effector domain/protein).

As a result, Fig. 2 provides a comprehensive overview of the currently known OSs collected in OPTICS, such as the sequence and typical 3D structure of photoreceptors, the range of sequence lengths and wavelengths, and so on. These data are essential for exploring the structure size, light responses, and the mechanisms of action, and thus are important for the rational design of new OSs [37]. Moreover, The number of OTs (Fig. 1C) and OSs (Fig. 1D) corresponding to each type of photoreceptor are as follows: opsins (186 OTs, 269 OSs), LOV domains (75 OTs, 196 OSs), cyanobacteriochromes (79 OTs, 81 OSs), phytochromes (29 OTs, 67 OSs), cryptochromes (13 OTs, 105 OSs), BLUF domains (5 OTs, 5 OSs), fluorescent proteins (3 OTs, 4 OSs), cobalamin binding domains (2 OTs, 3 OSs), and UV receptors (3 OTs, 3 OSs). These statistics reveal direct relationships between OTs and OSs.

2.2. Structural, spectral & functional data of OSs

2.2.1. Sequence and structure

For the nine-class photoreceptors, their fold types are completely different from each other (Fig. 2). While the diverse sequences engineered from the same class are often folded into similar 3D structure

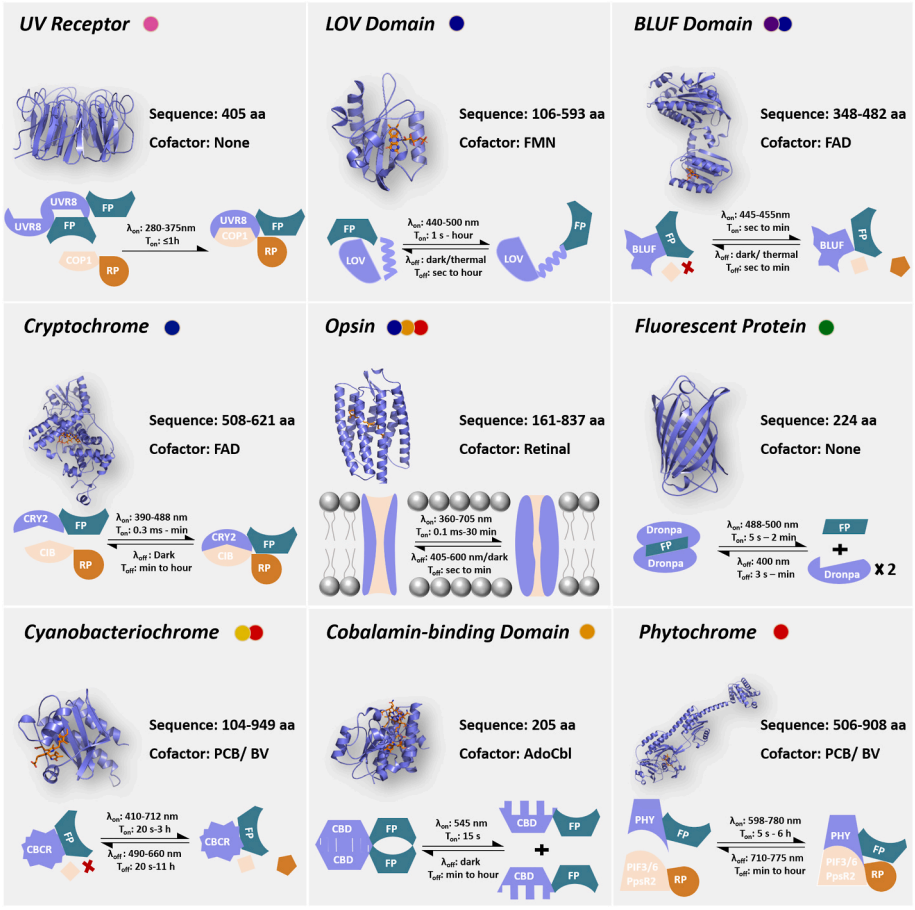

Fig. 2. Summary of optogenetic tools (OTs) refer to optogenetic systems (OSs) in OPTICS. OSs are classified into nine classes based on the OT and their mechanisms of action. They can be broadly divided into two main groups: light inducible dimerization (dark grey background) and conformational change (light grey background). Detailed information (light related information, representative 3D structure, PDB ID, cofactor, and protein sequence length) of each type is provided. λ_{on} and λ_{off} mean activation and deactivation wavelengths. T_{on} and T_{off} mean activation and deactivation times.

[26]. As shown in Fig. 3, 179 photoreceptors (ChR1, ChR2, VChR1, etc. discovered from several different organisms) from opsin exhibit a common architecture of seven transmembrane connected by three intracellular loops and three extracellular loops, with the retinal-binding pocket located at the transmembrane domain [38]. Nevertheless, naturally occurring photoreceptors with multidomain structures and large sizes have substantial drawbacks in optogenetic applications [39]. For example, the structures of BphPs (RpBphP1, RpBphP2, IsPadC, etc. discovered from different organisms) consist of several protein components [40] and could be redesigned as new OTs of single-component with smaller size [10]. In addition, for 11 complementary proteins and 12 cofactors of 396 OT, as well as 557 CPs, the sequences, and (or) structures data were collected in OPTICS, and the detailed information for each entry were provided on the corresponding webpage.

2.2.2. Wavelength and reversibility

Light induced conformational changes of photoreceptors in OTs are the structure basis for OSs to regulate a wide array of signaling pathways and molecular functions [2]. The collected OSs responding to light in living cells (Fig. 2) exhibit a wide range of wavelengths, ranging from blue (~450 nm) to yellow (~570 nm) to far-red (~740 nm). To activate the biological process in cell [4], each class of OSs has its own specific wavelengths of light (Fig. 2). Among the various wavelengths, the red light is particularly suitable for in vivo studies [41]. This is because the latter is weakly scattered by tissue and absorbed less by blood [42]. Therefore, the development of red light-sensitive OSs has become increasingly popular in recent years [41]. For example, a couple of red-shifted ChR variants have been engineered, and some of them (OS ID: OS00314, OS00337, and OS00372 in OPTICS) could be activated by orange to red light (~590–630 nm).

In addition to wavelength, reversibility is another important property when choosing an appropriate OS to manipulate the signals in space and time precisely [2]. Fig. 2 shows that, except for the UV receptor, the other seven classes have been successfully used to regulate reversible signaling pathways. As a result, 568 entries (73.86 %) collected in OPTICS are reversible OSs that have been tested in living cells. Moreover, to control cellular signaling more precisely, faster reversibility of an OS is needed [2]. Therefore, the speed of system reversal for each OS has been collected in OPTICS. As shown in Fig. 2, the time range varies from seconds (BphPs), tens of seconds (LOV domains) and minutes (CRY2) to hours (BphPs).

2.2.3. Signaling pathway and molecular function

On the basis of photoreceptor isolated from nature or engineered by rational design [30], OTs with varying light responses have been utilized to create OSs for the precise control of proteins that participated in a wide range of cellular functions [2]. OPTICS provides a comprehensive view of 212 signaling pathways and molecular functions modulated by 396 OTs. Taking CRY2-based OSs as an example, Fig. 4 illustrates the interaction network between OTs and CPs. In this network, four OTs (the wild type CRY2 and three variants CRY2 (L348F), CRY2 (L387A), and CRY2 (E490G)) interact with 53 CPs, which referred to biological processes at different levels including gene expression, kinase regulation, cell apoptosis, ion transport, protein translocation, and so on. The

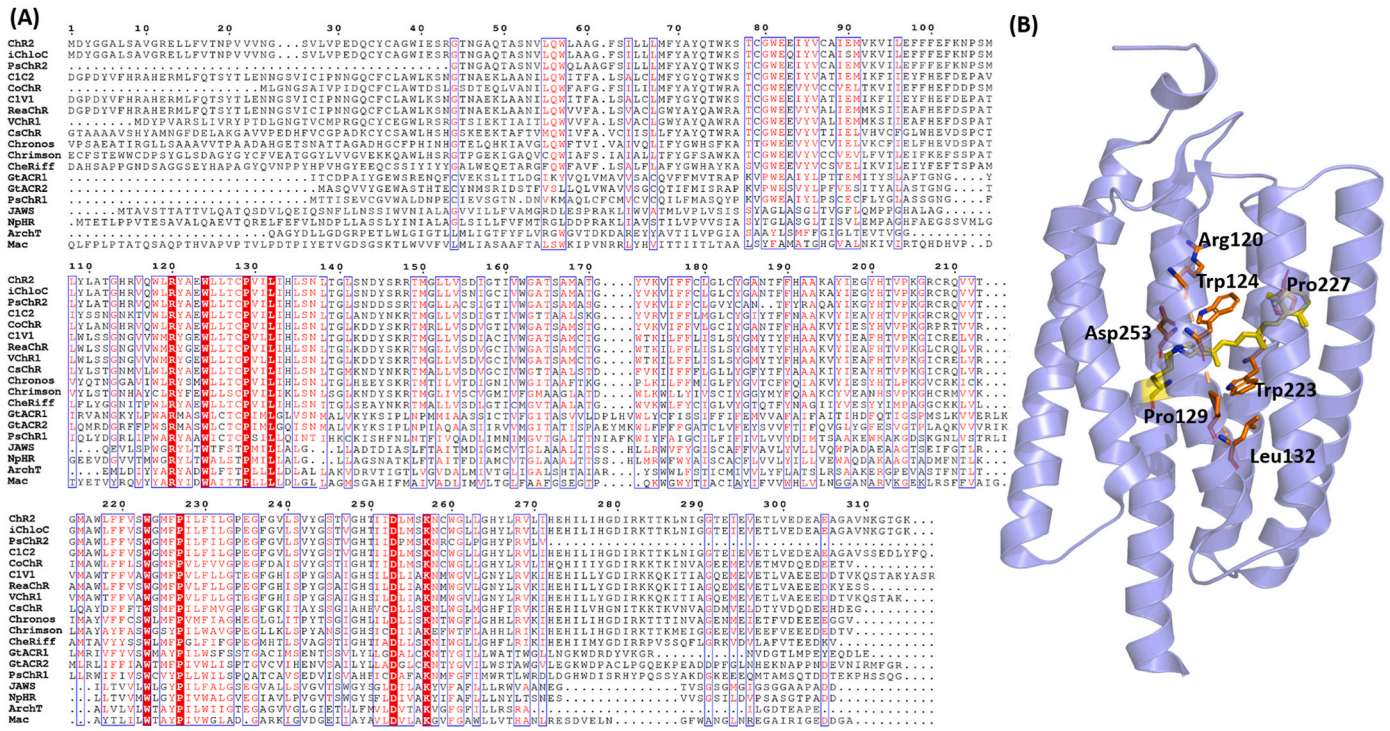

Fig. 3. Sequence and structure analysis of the channelrhodopsin and the cofactor. (A) Sequence alignment of opsin. (B) The 3D structure of channelrhodopsin 2 (PDB ID: 6EID), the protein (in light blue) is shown in cartoon, the cofactor (in yellow) and the conserved 8 residues (in orange, Retinal covalently attached to Lys257 via a protonated Schiff base) are shown in sticks.

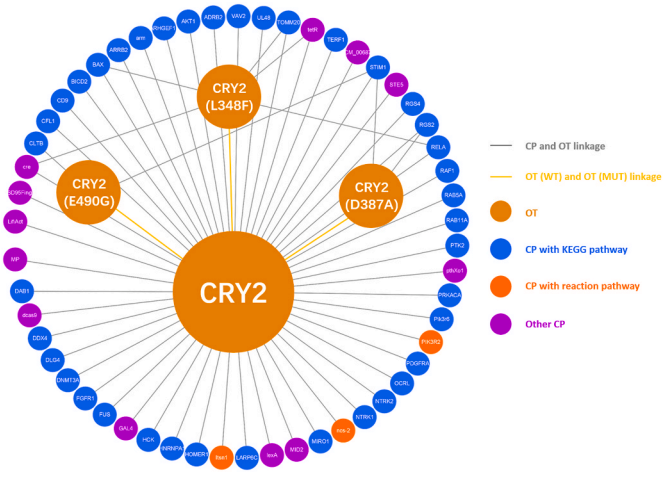

Fig. 4. The interaction network between the cryptochrome circadian regulator (CRY2) and the controlled proteins (CPs) calculated usuing Cytoscape. CRY2 represents one of the nine classes of optogenetic tools (OTs) in OPTICS, and the CPs are further mapped onto proteins with KEGG pathways, reaction pathways, and others by DAVID server.

information related to the cellular functions has been carefully annotated in OPTICS.

2.3. OSs' Application in research, diagnosis & therapy

The precise and spatiotemporal control of protein function by the innovative OS has rapidly developed over the past decades, greatly enriching the biological toolbox for dissecting cellular processes at the molecular level [34]. Furthermore, with the emergence of gene- and cell-based therapies [43], OSs have proven to be suitable for developing novel platforms that automatically link diagnosis and therapy (Fig. 5), thereby enhancing the safety and efficacy of therapeutic outcomes [4]. In OPTICS, detailed application, together with the light response information, are described on the corresponding webpages of a specific OS.

3. Conclusions

In sum, OPTICS is an online platform that offers systematic descriptions of up-to-date molecular biological data for a comprehensive set of OSs. The data collected in OPTICS database will pave the way for engineering and designing of next-generation OSs used to regulate various cellular and tissue physiologies in life science and human health. A user manual providing a step-by-step instruction on the usage of OPTICS is available on the "Help" page. We anticipate that our OPTICS, complementing to optogenetics-related databases (such as OptoBase, FPbase and FBDB), will serve as an important portal for users to fully utilize the most comprehensive and standardized data of OSs, and to facilitate the research in optogenetics community. All OSs data can be viewed, assessed, and downloaded from the OPTICS website, which is freely assessable without login requirement for all users at https://idrblab.org/optics/.

4. Materials and methods

4.1. Data collection

The data of OSs as well as their molecular modules (OTs and CPs) were collected through a literature review in PubMed [44]. First, by using the keyword combinations of photoreceptors family names (opsin, cryptochromes, LOV domain, fluorescent protein, phytochromes, cobalamin binding domain, BLUF domain, UV receptor, and cyanobacteriochromes) with 'optogenetics', e.g. 'opsin + optogenetics', 738 OSs were identified. Then, the detailed general information (name, OT, CP, and FP) and application information (mechanism of action, controlled signal pathway, light, and expression information) of each OS were further retrieved from literature. Third, 396 individual OTs and

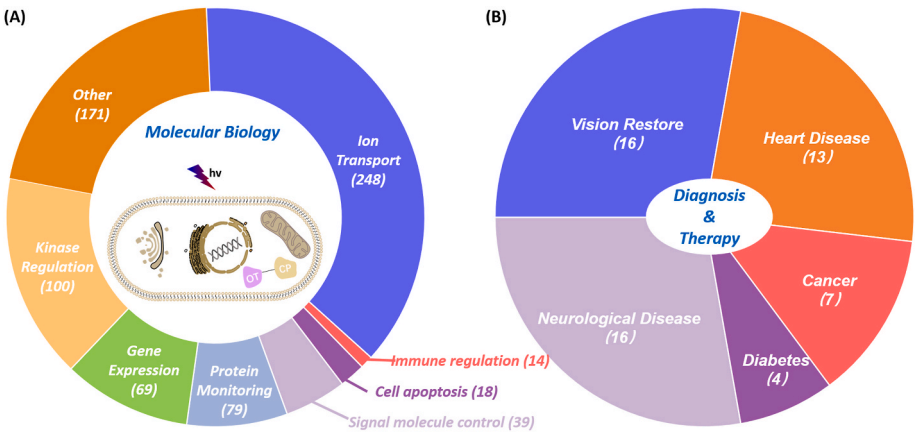

Fig. 5. The statistcs of current OSs' applications in OPTICS. (A) Outer layer: the number indicates the amount of OSs with the corresponding applications in molecular biology. Inner layer: a schematic of how the OS system regulates cell signals (OT and controlled protein are expressed in the targeted cell by transfection or other methods, and then the cells are illuminated with a particular wavelength). (B) The number indicates the amount of OSs with corresponding applications in disease diagnosis or therapy.

their key information (name, photoreceptor, cofactor, partner protein, sequence and mutation site of photoreceptor, 3D structure of photoreceptor, PubChem CID and structure of cofactor) were collected. The sequence and structure information of photoreceptor in each OS were obtained from UniProt [45], GenBank [46], and PDB [47]. For photoreceptors whose 3D structure information has not deposited in PDB [47], deep learning-based AlphaFold2 [48]was used for providing a predicted model [49]. Finally, the CP's information (name, sequence and pathway) for each OS was obtained through literature reviews and extended to UniProt [45] and KEGG [50].

4.2. Data standardization, access, and retrieval

To facilitate user access and analysis, the raw data of OPTICS were meticulously cleaned and systematically standardized. These standardizations included: (i) all OTs were standardized and crosslinked to available databases such as OptoBase [27], FPbase [28] as well as FBDB [1], and the extended data of each CPs could be accessed by hyperlinks to UniProt [45], GeneBank [46], PDB [47], KEGG [50], PubChem [51], etc., (ii) all OPTICS diseases were standardized according to the latest version of International Classification of Disease (ICD-11), officially released by World Health Organization [52], which is expected to serve comprehensive health managements [53], (iii) a light response properties based search against OSs in OPTICS was enabled to facilitate the design of OSs and their applications to new research fields. Furthermore, a user manual providing a step-by-step instruction for using OPTICS is available on the "Help" page, which can be easily accessed from the home page of OPTICS.

5. Data availability

The data in the OPTICS database are available athttps://idrblab.org/optics/. The data in other databases mentioned in this study were obtained from their websites (accessed in April 2024) or published papers: OptoBase (https://www.optobase.org/), UniProt (https://www.uniprot.org/), Genebank (https://www.ncbi.nlm.nih.gov/gene/), RCSB PDB (https://www.rcsb.org/), PubChem (https://pubchem.ncbi.nlm.nih.gov/), FPbase (https://www.fpbase.org/) and FBDB (https://biosensordb.ucsd.edu/).

CRediT authorship contribution statement

Zhao Zhang: Writing – original draft, Data curation. **Fengcheng Li:** Writing – review & editing, Visualization, Formal analysis. **Zixin Duan:** Validation, Methodology, Data curation. **Chaoqun Shi:** Data curation. **Xiaona Wang:** Methodology. **Feng Zhu:** Writing – review & editing, Resources, Conceptualization. **Weiwei Xue:** Writing – review & editing, Supervision, Resources, Methodology, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that there are no competing interests associated with the manuscript.

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