Developments in FRET- and BRET-Based Biosensors

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Contributor: Yuexin Wu , Tianyu Jiang

Resonance energy transfer technologies have achieved great success in the field of analysis. Particularly, fluorescence resonance energy transfer (FRET) and bioluminescence resonance energy transfer (BRET) provide strategies to design tools for sensing molecules and monitoring biological processes, which promote the development of biosensors.

fluorescence resonance energy transfer (FRET) bioluminescence resonance energy transfer (BRET) biosensors imaging

1. Biosensors for Biomedical Research

1.1. Biosensors for Bioassay and Diagnosis

FRET- and BRET-based biosensors are widely used for basic research on biological processes, such as signaling pathways, metabolism, and cell behavior, and to detect various substances of interest in organisms, both qualitatively and quantitatively. Biomarkers in the body, such as small molecules, nucleic acids, enzymes, proteins, antigens, hormones, metabolites, organelles, and cells, can be related to diseases and provide the possibility for precise and early diagnosis. Exosomes have been reported as valuable biomarkers associated with cancer-linked public health issues. For the quantitative detection of exosomes, Zhang et al. developed a self-standard ratiometric FRET nanoprobe, a Cy3-labeled CD63 aptamer (Cy3-CD63 aptamer)/Ti_3C_2 MXenes nanocomplex [1]. Without exosomes, the Cy3-CD63 aptamer could bind onto the Ti_3C_2 MXene nanosheets and FRET between the Cy3 and MXenes could cause the quench of the fluorescence signal from Cy3-CD63 aptamer. With added exosomes specifically combined with the aptamer and released from the surface of Ti_3C_2 MXenes, the fluorescence signal of Cy3 recovered. The hardly changed self-fluorescence signal of MXenes acted as a standard reference [1]. Krull et al. developed a FRET-based system for the sensitive screening of protein-based cancer biomarkers [2]. The aptamer-linked quantum dots (QDs-Apt) that could bind to the cancer biomarker protein epithelial cell adhesion molecule (EpCAM) was the donor and Cy3-labeled complementary DNA (cDNA) was the acceptor. With EpCAM competitive binding to QDs-Apt, the cDNA was displaced, resulting in the reduction of FRET [2].

In addition to biomarkers, other biological compounds, such as dopamine, have also attracted the attention of researchers. Liu et al. studied the secondary structure of a dopamine aptamer by isothermal titration calorimetry (ITC) and developed a biosensor for dopamine according to the resulting structure. A FAM fluorophore was labeled

on the 5′-end and a dark quencher was labeled on the 3′-end at the edited aptamer DNA. With dopamine, the two ends come together, resulting in fluorescence quenching by FRET [3]. Singh et al. developed the first biosensor for the monitoring of isoleucine in living cells named the genetically encoded isoleucine indicator (GEII). To construct the nanosensor, they linked a periplasmic binding protein (LivJ) of *E. coli* with the FRET donor and acceptor, ECFP and Venus. In the presence of isoleucine, FRET between ECFP and Venus could be observed. The GEII shows potential for application in the metabolic engineering of high isoleucine yield bacteria [4]. Chen et al. screened an aptamer against polysialic acid (PSA), Apt3, and employed it in a sensitive FRET-based biosensor for PSA [5]. Calamera et al. reported a set of high-affinity FRET-based cGMP biosensors containing fluorophores with different optical properties. The biosensors were applied to detect cGMP produced through soluble guanylyl cyclase and guanylyl cyclase A in stellate ganglion neurons and guanylyl cyclase B in cardiomyocytes for intracellular signaling studies [6]. Glutathione (GSH) is related to redox and mediates a large variety of biological processes. Its abnormal levels are associated with human disease. Zhang et al. designed a multi-signal ICT-FRET probe Mito-CM-BP, which could detect GSH and its metabolite sulfur dioxide (SO_2) simultaneously to visualize the metabolic processes of GSH to SO_2 in living cells [7]. They developed a coumarin–cyanoacetic acid (CM) system to visualize GSH dynamics where CM acted as the donor of the FRET-I process and CM-GSH was the donor of the FRET-II process. The sensitive reaction site for SO2, benzopyrylium unit (BP), was the energy acceptor [7]. Crocker et al. developed AMPfret, a genetically encoded nanosensor for the cellular energy state where the donor and acceptor FPs were linked to N- or C-terminus of the AMP-activated protein kinase (AMPK) [8]. The binding of AMP or ADP to the γ subunit of AMPK could cause conformational change of the sensor, resulting in a FRET signal change. This FRET-based biosensor could detect changes in ATP/ADP and ATP/AMP ratios both in vitro and in cellulo [8].

The demand for portable, rapid, and sensitive detection at the point-of-care (POC) has grown for applications, such as early diagnosis of diseases and health monitoring of patients. RET-based biosensors, especially biosensors based on BRET where external light excitation is not necessary, have been put into POC applications. This progress has been well described by a comprehensive review [9]. One direction of POC applications is the quantitative detection of drug concentrations in the blood of patients. In 2014, a series of NanoLuc-based BRET-sensor proteins for the detection of small-molecule drugs (luciferase-based indicators of drugs, LUCIDs) were reported [10]. In designing the sensor, the anticancer agent methotrexate was chosen as the analyte. Bacterial dihydrofolate reductase (DHFR) was used as a receptor protein, and the DHFR inhibitor trimethoprim was the intramolecular ligand. The sensor was a fusion protein SNAP-Pro30-NanoLuc (NLuc)-cpDHFR linked to a synthetic molecule containing Cy3 and a DHFR inhibitor. With an analyte, the sensor could be shifted to an open conformation, reducing BRET efficiency. LUCIDs could monitor different drugs, such as the immunosuppressants tacrolimus and sirolimus, cyclosporin A, the antiepileptic topiramate, and cardiac glycoside digoxin [10]. RET-based biosensors have been applied for the detection of antibodies. In 2016, Arts et al. developed BRET-based single-protein sensors named LUMinescent AntiBody Sensors (LUMABS) consisting of a semiflexible linker between the donor NanoLuc and the acceptor green fluorescent protein mNeonGreen [11]. Helper domains keep the donor and acceptor close without the antibody of interest. When an antibody binds to epitope sequences flanking the linker, the interaction between the helper domains is disrupted, and the BRET efficiency decreases showing change in color from green-blue of the acceptor to blue of the donor. This provided the technology to easily measure

picomolar antibody concentrations with a smartphone without the washing step. Not only can LUMABS recognize natural peptide epitopes, but they can also recognize nonpeptide epitopes. LUMABS sensors have been applied to the detection of antibodies against HIV1-p17, antibodies against hemagglutinin (HA), antibodies against dengue virus type I, dinitrophenol, creatinine, the Her2-receptor targeting trastuzumab, the anti-CD20 antibodies rituximab and obinutuzumab, and the EGFR-blocking cetuximab [11][12][13]. Based on LUMABS, Tenda et al. developed the first fully integrated microfluidic paper-based user-friendly analytical devices (μPADs) [14]. The BRET-based LUMABS was fixed into the device, which sensed the object of interest and produced color changes that could be captured by a digital camera. Researchers have provided opportunities for simultaneous detection of three different antibodies (anti-HIV1, anti-HA, and anti-DEN1) in whole blood in a highly user-friendly “just add the sample” manner [14]. By competitive intramolecular complementation of split NanoLuc, a new sensor format, NB-LUMABS, was reported in 2019 [15]. Two copies of a 1.3 kDa small BiT (SB) of NanoLuc were fused to either the N- or C-terminus of a single copy of an 18 kDa large BiT (LB) of NanoLuc to form a protein switch, while only SB on the N-terminus was conjugated to Cy3 for the emission of red light. Without antibody, the switch formed the conformation where the N-terminal SB binds to the LB and reconstitutes luciferase activity that allows for the BRET process to emit red light. This conformation can be disrupted by bivalent binding of an antibody resulting in nonfluorescently labeled SB combined with LB emitting blue light [15]. Takahashi et al. developed a BRET Q-body, in which luciferase NanoLuc is fused to a Q-body to construct a new immunosensor [16]. Quenchbodies (Q-bodies) are antibody fragments comprising an antibody fragment containing an antigen-binding site that is site-specifically labeled with a fluorescent dye. NLuc was fused to the N- or C-terminus of a single-chain antibody (scFv) fragment that specifically binds osteocalcin (bone Gla-protein, BGP) and then was labeled with ATTO520-C2-maleimide. In the presence of the antigen BGP-C7, the quenched fluorescent dye is released, and thus, NLuc oxidizes the luminescent substrate to provide energy transferring to the now available dye. A 12-fold higher response was acquired, implying that BRET Q-body is a useful biosensor in point-of-care tests [16]. Monitoring of biomarker metabolites is of great significance for the diagnosis, treatment, and management of numerous diseases. Yu et al. developed a biosensor that can measure NADPH by a digital camera in paper-based assays [17]. A fluorescently labeled ligand with NADPH-dependent affinity for the receptor is covalently tethered to the NADPH-dependent receptor protein through SNAP-tag. Without NADPH, the sensor is in an open state where the ligand could not bind to the receptor. The addition of NADPH could trigger the formation of the closed state where the binding of ligand and receptor brings the acceptor Cy3 close to NanoLuc, thereby increasing BRET. The NADPH concentration could be quantitatively calculated from the ratio of the emission intensities of NanoLuc and Cy3. This biosensor was applied for assay for phenylketonuria (PKU) with whole-blood samples [17]. Li et al. developed a paper-based BRET system for the analysis of tumor-associated circulating microRNAs (miRNAs) in clinical serum samples [18].

1.2. Biosensors for In Vivo Imaging

FRET- and BRET-based biosensors are widely used in in vitro and in vivo imaging and the analysis of biological compounds, making it possible to visualize various biological processes.

Yang et al. developed a BRET-based genetically encoded Ca^{2+} sensor that does not need external excitation, coordinating it with optogenetics techniques [19]. The troponin C domain (TnC) was inserted between C-terminal

truncated Venus and NanoLuc luciferase. In the presence of Ca^{2+}, the conformational change of the Ca^{2+}-sensitive troponin sequence brought NanoLuc closer to Venus so that BRET could occur, resulting in a concomitant spectral shift. They put the sensor into quantifying and imaging Ca^{2+} fluxes elicited by brief pulses of light to cultured cells expressing melanopsin and to the neurons-expressing channel rhodopsin. The utilization of BRET sensors that do not need external excitation helps to eliminate undesirable consequences of fluorescence irradiation [19].

Adenosine 3′,5′-cyclic monophosphate (cAMP) is an important second messenger regulating plenty of intracellular functions. A classic example of studying the cAMP signaling pathway in cells is the sensor FlCRhR, which was the first FRET-based biosensor for cAMPs. It consists of cAMP-dependent catalytic subunits of protein kinase A I (PKA I), in which the catalytic (C) and regulatory (R) subunits are each labeled with fluorescent dye fluorescein or rhodamine, and FRET is shown in the holoenzyme complex R_2C_2. The C subunits could dissociate from the complex with cAMP bound to the R subunits, and the energy transfer is thus reduced [20]. However, chemically labeled proteins are unstable and hard to produce. They have to be microinjected into cells instead of expressed in cells, which could affect cAMP kinetics [21]. The traditional fluorescein- and rhodamine-labeled FlCRhR sensor was modified with BFP and GFP by Zaccolo et al. in 2000 [22], and then with CFP and YFP in 2002 [23]. These works make FlCRhR genetically encoded, and microinjection is not needed. The use of FPs allows for the elucidation of the biochemistry of cAMPs in vivo. FlCRhR was put into use for several different applications related to cAMPs, such as imaging cAMPs in neurons and neuronal networks [24] and the study of cAMP dynamics in oocytes [25][26]. Nagai et al. reported a cAMP-responsive tracer (ART) for visualizing the phosphorylation of proteins in living cells in 2000. It was the first FRET biosensor for protein kinases. Two GFP variants, RGFP and BGFP, were linked through the kinase-inducible domain (KID) of the transcription factor cAMP-responsive element binding protein (CREB). With PKA phosphorylation, the FRET among the flanking GFPs decreased [27]. For the detection of ATP, a BRET sensor was created by Min et al. named ARSeNL, ATP detection with a ratiometric mScarlet-NanoLuc sensor [28]. This biosensor employed a combination of NanoLuc and mScarlet as the donor and acceptor and showed a large dynamic range in detecting ATP. It was proposed that the development of ARSeNL could expand the toolbox of in vivo imaging of the metabolic status [28]. Shcherbakova et al. used a new red-shifted monomeric NIR fluorescent protein, miRFP720, to construct a FRET pair of miRFP670–miRFP720 for multiplexed imaging and light control of the Rho GTPase signaling pathway [29]. The development of miRFP670–miRFP720 pair enabled the further design of biosensors compatible with CFP-YFP imaging and blue-green optogenetic tools in use [29].

FRET- and BRET-based biosensors have been applied for in situ dynamic tumor microenvironment visualization. Zhao et al. reported on serial pH_t adjustable sensors (pTAS) for tumor pH monitoring [30]. The higher sensitivity and wider response region of these sensors were achieved by regulation of the component ratio of the second near-infrared (NIR-II) emission aza-BODIPY (NAB) donor and pH-sensitive rhodamine-based pre-acceptor (NRh). The sensor achieved dynamic visualization of in vivo tumor pH change processes through dual-channel ratiometric bioimaging within the NIR-II window [30].

2. Biosensors for Environmental Applications

FRET- and BRET-based biosensors are used in the detection of toxic small molecules in food and the environment. Tang et al. designed a nanobody-mediated immunosensor based on FRET between different-sized QDs [31]. QDs of two sizes were covalently labeled with OTA and Nb, acting as the energy donor and acceptor. Both the free OTA and the donor could bind to the acceptor. When OTA concentration increased, the FRET efficiency decreased for less donor bonded to the acceptor. The sensor allowed rapid detection of OTA in agto-products in 5 min with a detection limit of 5 pg/mL [31]. Sabet et al. developed a FRET-based sensor for the detection of aflatoxin B1 (AFB1) [32]. The QDs conjugated with aptamer in the sensor were quenched via FRET without AFB1 due to the interaction of the aptamers with AuNPs. The aptamers were attracted to the added AFB1 from the AuNPs, and the fluorescence could recover. The developed biosensor was applied for the analysis of AFB1 in rice and peanut samples [32]. A series of biosensors based on FRET for the determination of organophosphate pesticides were designed by Wu et al. [33]. The fluorescence emission of carbon quantum dots (CQDs) could be quenched by AuNPs. Butyrylcholinesterase (BChE) could hydrolyze acetylthiocholine (ATC) to produce thiocholine, which could cause the aggregation of AuNPs and the corresponding recovery of FRET-quenched fluorescence emission. With the organophosphorus pesticides (OPs), the recovery of fluorescence in the sensor was reduced owing to the irreversibly inhibited catalytic activity of the BChE by the OPs. The biosensor was applied for OP detection in tap and river water samples [33].

Heavy metals are one of the environmental pollutants researchers aim to detect. For the detection of Hg^{2+}, Li et al. developed a turn-on nanosensor based on FRET between long-strand aptamer-functionalized UCNPs and short-strand aptamer-functionalized gold nanoparticles (GNPs) [34]. The UCNPs were initially quenched due to the specific matching between the two aptamers. The stable binding interactions between Hg^{2+} and thymine could induce the long-stranded aptamers to fold back forming a hairpin structure. This caused GNPs to release from the UCNPs, and the fluorescent signal recovered. The sensor was applied to detect Hg^{2+} in tap water and milk samples [34]. Liu et al. employed gold nanorods (Au NRs) as the energy acceptor and CDs as the donor to construct a biosensor for Pb^{2+}. The Au NRs were absorbed on the surface of the CDs, resulting in a quenched fluorescence signal of the CD–cysteamine–Au NR assembly. The Pb^{2+} ions bound completely with the cysteamine and disturbed the FRET process, and the fluorescence signal was restored. The sensor performed well in the detection of Pb^{2+} ions in samples of tap water and river water samples [35].

In addition to pollutants, there is also concern about pathogenic microorganisms in the environment. Jin et al. developed a novel detection platform based on FRET for specific bacteria detection in the environment and food [36]. Upconversion nanoparticles (UCNPs) acted as the donor and were functionalized with the corresponding cDNA. The acceptor AuNPs that could cause fluorescence quenching were conjugated with aptamers. Without target bacteria, the aptamers bound to the cDNA, resulting in a quenching of the UCNPs. With the bacteria of interest, the aptamers preferentially bound to the bacteria rather than the cDNA to dissociate UCNPs–cDNA from the AuNP–aptamers, and the upconversion fluorescence would recover. The sensor was proved to efficiently detect *E. coli* in real food and water samples such as milk and tap/pond water within 20 min [36].

3. Biosensors for In Vivo Dynamic Analysis of Metabolic Flux

Metabolic flux is of great importance in metabolic engineering and facilitates the study of biosynthetic pathways. To precisely control the engineered system and obtain an improved metabolite flux, measuring the metabolites concentrations and flux rates and metabolic intermediates is a vital part of synthetic biology [37]. Many biosensors have been developed to address this problem, among which are RET-based biosensors.

Engineering microbial strains to produce L-lysine draw scientists' attention in industrial biotechnology. Thus, Ameen et al. developed a series of genetically encoded FRET-based nanosensors, namely FLIPK for the real-time monitoring of lysine at a cellular level [37]. The lysine binding periplasmic protein (LAO) from the *Salmonella enterica serovar typhimurium* LT2 strain was utilized as a part of a reporter, which was sandwiched between CFPs and YFPs. They tested the sensors for successfully monitoring the intracellular level of lysine both in bacterial and yeast cells and concluded that the sensors can be applied for the in vivo measurement of lysine levels in eukaryotes as well as prokaryotes. The sensors could be further used to measure real-time intracellular lysine levels in metabolically engineered microbial strains [37].

In order to analyze the metabolic flux of the (+)-catechin biosynthetic pathway, Kausar et al. developed a fluorescence indicator protein named FLIP-Cat, a FRET-based nanosensor for in vivo real-time monitoring of the metabolic flux of the (+)-catechin [38]. This genetically encoded nanosensor was composed of a (+)-catechin binding protein fraa-3 from *Fragaria ananassa* as a ligand-sensing domain, ECFP as the donor, and Venus as the acceptor. The donor ECFP was linked to the N-terminus of the fraa-3 protein, and the acceptor YFP was fused to the C-terminus of the fraa-3 protein. With the binding of the (+)-catechin, the fraa-3 protein underwent conformational changes for FRET to occur. The researchers then designed a (+)-catechin biosynthesis pathway and introduced it in *E. coli* along with the biosensor FLIP-Cat. With addition of different substrates, they measured the metabolic flux of the (+)-catechin in real-time and identified that dihydroflavonol reductase (DFR) was the main regulatory element. DRF can be utilized for controlling the (+)-catechin biosynthetic pathway, thus enhancing the production of catechin [38]. FRET- and BRET-based biosensors have good performance in monitoring metabolic processes according to the previous study. This could increase researchers' understanding of specific processes and help researchers engineer metabolic processes, which is of great significance in synthetic biology research related to metabolic engineering.

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