ADVANCED ELECTRONIC MATERIALS
www.advelectronicmat.de

A Novel Biomimetic Magnetosensor Based on Magneto-Optically Involved Conformational Variation of MagR/Cry4 Complex

Le Xue, Tao Hu, Zhen Guo, Celi Yang, Zhuoqing Wang, Siying Qin, Peilin Yang, Can Xie, Jian Xu, Nuan Li, Yanfei Shen, Hui Jiang, Dawei Deng, Ning Gu, and Jianfei Sun**

During billions of years of evolution, some species develop fantastic magneto-perception, offering a biomimetic route to develop the next generation of magneto-sensors. Recently, a novel principle was proposed to explain the navigation of pigeons in the presence of geomagnetic fields and sunlight. The key link is thought to lie in the magneto-optically involved conformational variation of magnetoreceptor protein (MagR)/cryptochrome (Cry4) complex. The MagR/Cry4 complex is fabricated and purified in vitro, creating a magneto-sensing device by immobilization of this protein on a graphene-modified electrochemical electrode. By using electrochemical impedance spectroscopy, magneto-sensing with a current detectability of 10 mT is realized with MagR/Cry4 complex. It is proved that this process requires the involvement of both magnetic fields and light, partly confirming in vitro the magneto-perceptive mechanism of MagR/Cry4 complex. It is also shows that this device can be used to reflect the anisotropic responses of nanomaterials to the external magnetic field. It is believed this protein-based magneto-sensing will greatly boost development of bioelectronics and deepen understanding of the phenomena of magneto-perception for organisms.

All creatures on the earth have evolved in the presence of magnetic field. Investigation about magneto-perception and biological effects of magnetic field will be greatly beneficial to understanding the evolution of life and innovation of physical therapy.[1] Here, the principal issue is to sense the magnetic field. From the discovery of electromagnetic induction to the quantum Hall effect, humans have strived for seeking applicability of novel mechanisms in the magneto-sensors.[2] Currently, the magneto-sensors are generally based on the quantum effects, which relies on a highly sensitive interface of semiconductor materials commonly fabricated by epitaxial growth.[3] With development of flexible electronics and bioelectronics, these semiconductor based technics seem increasingly unsuitable for the biomedical applications.

Interestingly, some species possess an amazing capability of magneto-perception such as migratory birds,[4] butterflies,[5] and honeybees.[6] These animals perceive the geomagnetic field relying on special proteins. Cryptochrome (Cry) has been considered for a long time to mediate the magneto-perception via quantum spin dynamics of light-induced radical-pair, which are excited by sunlight and can be modulated by the geomagnetic field.[7–9] This principle was employed to sense the magnetic field because the life-time and the spectral characteristic of radical pair in singlet and triplet states can reflect the information about magnetic field.[10] Cry played an important role in the

L. Xue, N. Li, Prof. N. Gu, Prof. J. Sun
Jiangsu Key Laboratory of Biomaterials and Devices
School of Biological Science and Medical Engineering
Southeast University
Nanjing 210009, P. R. China
E-mail: guning@seu.edu.cn; sunzaghi@seu.edu.cn

L. Xue, N. Li, Prof. H. Jiang, Prof. N. Gu, Prof. J. Sun
State Key Laboratory of Bioelectronics
Southeast University
Nanjing 210096, P. R. China

L. Xue, Prof. D. Deng
Department of Biomedical Engineering
School of Engineering
China Pharmaceutical University
Nanjing 210009, P. R. China

The ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/aelm.201901168.

DOI: 10.1002/aelm.201901168

Prof. T. Hu, J. Xu
School of Mechanic Engineering
Southeast University
Nanjing 211189, P. R. China

Z. Guo, C. Yang, Z. Wang, Dr. S. Qin, P. Yang, Prof. C. Xie
State Key Laboratory of Membrane Biology
Laboratory of Molecular Biophysics
School of Life Sciences
Peking University
Beijing 100871, P. R. China

Prof. C. Xie
Beijing Computational Science Research Center
The Chinese Academy of Engineering Physics
Beijing 100084, P. R. China

Prof. Y. Shen
Department of Bioengineering
School of Medicine
Southeast University
Nanjing 210009, P. R. China

magnetic sensing system of some species.[11] A simplified artificial macromolecule containing a single tryptophan residue from a covalently bound flavin was synthesized.[12] With this synthetic compound, 20 mT magnetic field was measured with the transient spectrum. However, this mechanism remains incapable of explaining all the magneto-perceptive phenomena. In 2015, one novel mechanism was proposed in which the magnetoreceptor protein (MagR)/Cry4 complex was considered to play a key role.[13] A so-called MagR protein, that is, IscA-1, a member of iron–sulfur cluster assembly protein family was identified capable of transferring electrons to the Cry4 under treatment of the magnetic field, then causing the variation of molecular conformation of Cry4 to activate the downstream signal pathway. This phenomenon suggests a novel biomimetic strategy for the magneto-sensing.

Here, we employed the entirely natural MagR/Cry4 complex to make up a magneto-sensor based on this novel principle of magneto-perception. A three-electrode electrochemical system was constructed in a microfluidic chip with the MagR/Cry4 complex assembled on the electrode. We proposed to exploit the electrochemical impedance to reflect the variation of external magnetic field. It was discovered that only the MagR/Cry4 complex can show the significant response to magnetic field in the presence of light. This device can realize the detection of 10 mT magnetic field and clearly show the anisotropic difference of nanoparticulate assemblies in magnetic responding. These results conceptually validated feasibility of the biomolecular magneto-sensing and partly proved the MagR/Cry4 complex-based principle of magneto-perception. We believe this work will greatly boost the development of bioelectronics and magneto-sensor, deepening the understanding about natural magneto-perception.

Preparation process of both proteins was schematically shown in **Figure 1**a. In our experiments, 700 mL Luria–Bertani(LB) medium can yield 5 mL MagR protein (1–1.5 mg mL^{-1}) and 0.25 mL MagR/Cry4 complex (0.2–0.4 mg mL^{-1}), respectively. After expression and purification, the MagR and MagR/Cry4 complex were identified by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and ultraviolet and visible spectroscopy. The results were nearly identical with those in ref. [13] (Figure S1, Supporting Information), indicating that we accomplished the production of purified proteins in vitro. The MagR and MagR/Cry4 complex were further characterized with TEM (Transmission Electronic Microscopy) and DLS (Dynamic Light Scattering) (Figure 1b,c). The DLS size of MagR/Cry4 complex was about 18 nm, which was in accordance with that of TEM. Interestingly, the size and morphology of MagR monomers seemed similar with those of MagR/Cry4 complex, which was thought to mainly result from the sample preparation process of lyopilization rather than crystallization.

Although the intrinsic magnetic properties of MagR protein and MagR/Cry4 complex have been reported,[13,14] we experimentally measured the magnetic properties of the MagR protein, the MagR/Cry4 complex and the controls by ESR (Electron Spin Resonance) spectroscopy. ESR is a sensitive, fast, and sample-economic method for magnetic measurement. However, the MagR protein and MagR/Cry4 complex showed no difference with other materials at 298 K (Figure S2, Supporting Information). This case meant the magnetic moments of MagR protein and the MagR/Cry4 complex were so weak that the thermal fluctuation can facilely destroy their couplings.[15] Thus, at room temperature, the MagR protein and MagR/Cry4 complex were paramagnetic. The maximal magnetic strength can be theoretically estimated to be 2×10^{-21} J T^{-1}.[15] The ferromagnetic contamination of proteins was excluded by detection of Fe concentration of buffer for purification of MagR protein and MagR/Cry4 complex using ICP-OES (Inductively Coupled Plasma Optical Emission Spectrometer). There was scarcely exogenous Fe in the buffer used for purification while the solution of protein containing 40 μM MagR showed significant iron content (Figure S3, Supporting Information). Thus, the proteins were not contaminated by Fe-based matters. The detailed magnetic property of MagR protein and MagR/Cry4 complex should be further explored in the future.

Based on the hypothesis that the magnetic field can cause the electron transfer and conformational variation of MagR/Cry4 complex, we thought this process somewhat resembled common redox reaction. The electrochemical method has been used to investigate the redox process and it is suitable to detect properties of the working electrode. MagR/Cry4 complex modified on the surface of electrode could affect its own state by magnetic field, which resulting in the changes of dielectric and conductive properties of the working electrode. Therefore, we chose the electrochemistry to detect the magnetic field. The three-electrode system is a standard configuration for electrochemical detection so that we constructed our device in vitro as the three-electrode system. The gold electrodes were modified with the MagR and the MagR/Cry4 complex, respectively (Figure S4a, Supporting Information) for measurement with cyclic voltammetry (CV) method in the presence of magnetic field. It was discovered that the modification of protein molecules significantly reduced the conductivity of electrodes. However, there was no significant alteration of the CV curve with and without treatment of a magnetic field (Figure S4b,c, Supporting Information). Initially, we thought this case may result from the influence of electrolyte. Based on the possible mechanism of magneto-perception, light is necessary for the electron transfer. However, the $K_3[Fe(CN)_6]/K_4[Fe(CN)_6]$ solution has a strong absorption at blue wavelength. Traditional electrolyte cell seems too large to avert this influence. Thus, a microfluidic chip was designed to perform the electrochemical measurements with the three-electrode system (**Figure 2**a) and the photograph was shown in Figure 2b. Depth of the channel was about 80 μm which can greatly reduce the light path effectively minimizing the light absorption of electrolyte. In this device, the surface of WE (working electrode) was the 1-pyrenecarboxylic acid-doped rGO (reduced graphene oxide), which showed a multilayer structure with depth of 5 μm (Figure S5, Supporting Information). The protein immobilization on this surface was based on the 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC)/N-hydroxysuccinimide (NHS) chemistry, schematically shown in Figure 2c. During the experiments, this device was put inside a shielding box. Then, the electrochemical measurements were carried out free from electromagnetic interference and in the presence of white light (Figure 2d). However, there remained insignificant difference in the CV curves with and without the treatment of magnetic field (Figure S6, Supporting Information). This case was thought to result from the localized transfer of electrons. The electrons can just transfer from the MagR molecules to the Cry4 molecules rather than the long-ranged transport. Thus, it was unable to influence the loop current of electrochemical system.

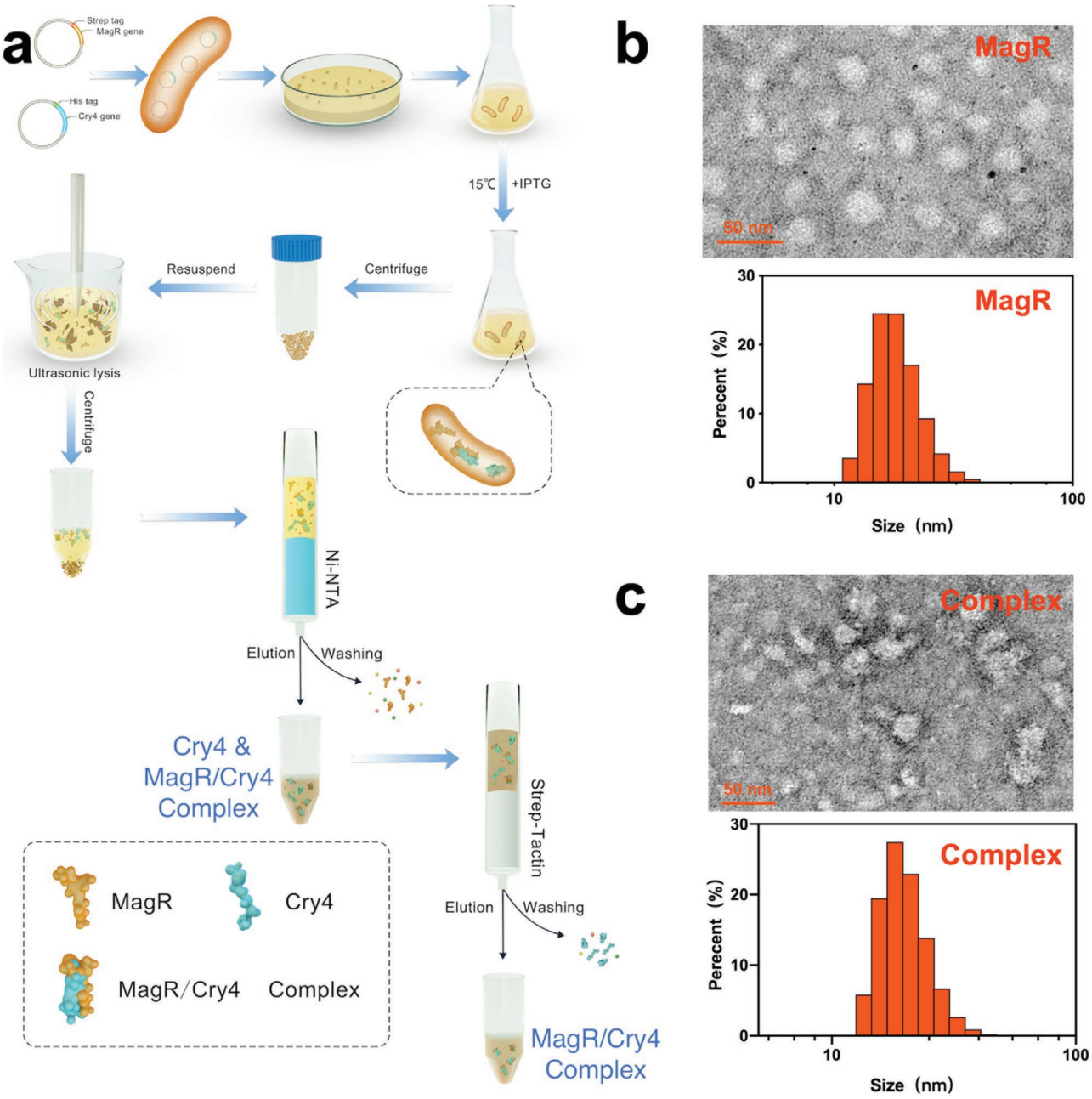

Figure 1. Production and Purification of proteins in vitro. a) Schematic show of preparation process. b) TEM image and DLS measurement of MagR. c) TEM image and DLS measurement of MagR/Cry4 complex.

Fortunately, the magneto–perception also causes the conformation alteration of Cry4 molecules in addition to the electron transfer. This alteration can get reflected by the electrochemical impedance spectroscopy (EIS). Compared with CV method, the EIS can exhibit more dynamic information with a linear response to small amplitude disturbance.[16] The EIS of molecules can be often described by the Randles model,[17] which contains four elements: the electrolyte solution resistance (R_s), the charge transfer resistance (R_{ct}), the constant phase element (CPE), and the Warburge impedance (Z_w).[18] Here, R_s and Z_w demonstrate integral property of the solution while R_{ct} and CPE are affected by property at interface between the electrode and the electrolyte. In the Nyquist diagram, the semicircular portion represents the electric double layer capacitance, the diameter of the semicircle is equal to R_{ct}, and the linear portion represents the impedance change caused by ion diffusion in the solution. **Figure 3**a,b schematically showed equivalent circuit models of the electrochemical detection system and the MagR/Cry4 complex, respectively. In the presence of magnetic field, for one thing, the magnetic moments of MagR can be aligned so that the process of charge transfer will be different to change the impedance. For another, the molecular conformation of Cry4 may be changed after the

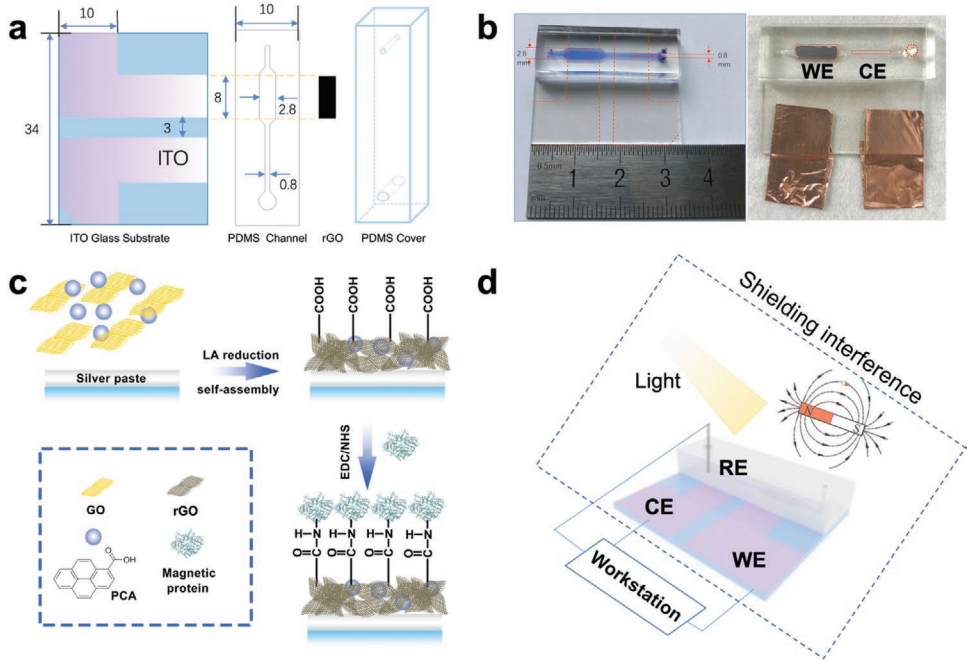

Figure 2. Scheme of the MagR/Cry4 complex-based device for detection of magnetic field. a) Structural illustration of the microfluidic chip; b) Photograph of the three-electrode device (the blue indicated the channel); c) Schematic show of protein immobilization on electrode surface; d) Experimental illustration for detection of magnetic field.

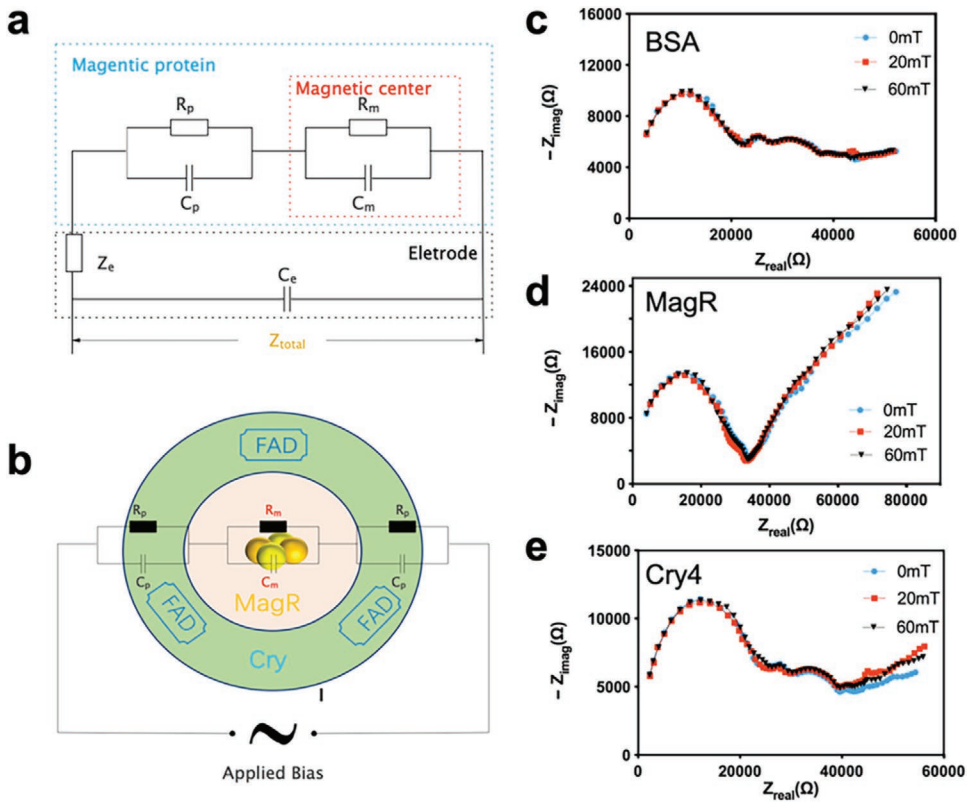

Figure 3. Electrochemical impedance spectra of the protein-based device. a,b) Scheme of the equivalent circuits for electrode system and MagR/Cry4 complex. c–e) EIS for the detection of magnetic field with BSA-modified WE, MagR-modified WE and Cry4-modified WE, respectively, which can prove the magnetic specificity of our device.

activation of MagR. This will also influence the impedance. To validate the molecular variation under the treatment of magnetic field, we preliminarily exploited the SFG (summed frequency generation) spectrum to investigate the variation of molecular conformation for the MagR molecules. SFG is a highly sensitive spectroscopic means to see molecular orientation at solid–liquid interface.[19,20] Seen from the results (Figure S7, Supporting Information), there was a clear difference for the protein after the treatment of magnetic field, indicating the conformational variation. Thus, we believe the EIS is feasible in the sensing of magnetic field. In our experiments, R_{ct} was chosen as the indicant to show the magnetic sensing. Besides the experimental data, the Nyquist diagrams were also simulated by Zview software. It can be seen from the experimental figures that the simulated results matched the experimental data very well, meaning the Randles model is applicable here.

We first excluded the influence from the graphene on substrate because it was recently reported to exhibit the Hall effect.[21,22] This case possibly interfered with the detection results. As shown in Figure S8a, Supporting Information, there was nearly no difference for the rGO film after imposing 20 mT magnetic field. Moreover, it was calculated based on the EIS data that the R_{ct} of bare rGO electrode was about 8 kΩ, which was stable during the experiment of even 60 mT field (Figure S8b, Supporting Information). Meanwhile, bovine serum albumin (BSA) was used to validate the magnetic specificity. It was found there was also no variation in the EIS curves (Figure 3c). Thus, the device was suitable for magnetic detection. The experimental results confirmed the role of MagR/Cry4 complex in vitro. If only the MagR was modified on the WE, there remained nearly no variation after imposing even the 60 mT magnetic field (Figure 3d). The identical case was seen for the only Cry4-modified WE (Figure 3e). These results demonstrated in vitro that neither the MagR nor the Cry4 was incapable of responding to the external magnetic field.

However, if the MagR/Cry4 complex was modified on the WE, the EIS exhibited a strong relationship with the intensity of external field. As shown in **Figure 4**a, the R_{ct} (semicircular

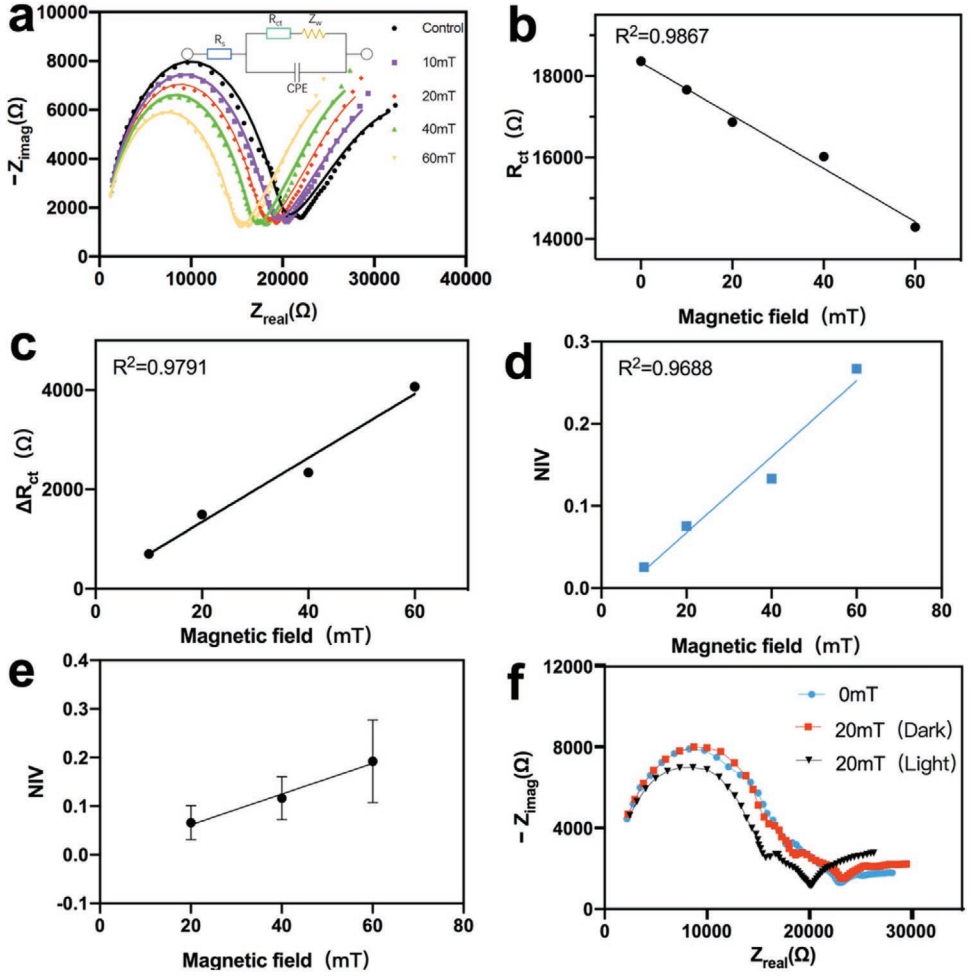

Figure 4. Magneto-sensing with the MagR/Cry4 complex-based device. a) EIS for the detection of magnetic field with MagR/Cry4 complex-modified WE without and with treatment of different magnetic field. b) Linearity correlation between the R_{ct} and the intensity of magnetic field. c) Linearity correlation between the ΔR_{ct} and the intensity of magnetic field. d) Linearity correlation between the normalized ΔR_{ct} and the intensity of magnetic field. e) Statistical plot of the NIVs from 20 mT to 60 mT. f) EIS of MagR/Cry4 Complex-modified WE in the presence and the absence of magnetic field and light. It can be seen the light is necessary for sensing of magnetic field with the MagR/Cry4 complex.

diameter of the EIS) was found to positively reduce with increase of the field intensity. The linear correlation coefficient was 0.9867 (Figure 4b). Moreover, we defined $\Delta R_{ct} = R_{ct}^0 - R_{ct}$, where R_{ct}^0 represented the R_{ct} without the magnetic field. The ΔR_{ct} also showed good linear correlation (0.9791) with the intensity of magnetic field (Figure 4c). We further defined the normalized impedance variation $\text{NIV} = \frac{R_{ct}^0 - R_{ct}}{R_{ct}}$. The linear correlation coefficient between the NIV and the intensity of magnetic field was 0.9688 (Figure 4d). Thus, this dimensionless unit can also be used as the indicator of magneto-sensing. It was found under the case of multiple duplicated experiments, the NIV still showed good linearity ranging from 20 to 60 mT. The statistical result was shown in Figure 4e. However, for 10 mT field, the detection result occurred a certain deviation. The linear correlation coefficient decreased to 0.6844 (Figure S9, Supporting Information), partly meaning the applicability of this protein-based device in sensing of magnetic field. The natural magneto-perception in organisms may be a non-linear responding process.

With this sensing experiment in vitro, it was also demonstrated the role of light for the magneto-perception of MagR/Cry4 complex. It was found the MagR/Cry4 complex was incapable of causing the variation of EIS in absence of light (Figure 4e). This case partly proved the magneto–optical coupling mechanism of MagR/Cry4 complex in biological magneto-perception.[13] The light is necessary for the activation of Cry4. Finally, we tried to use this device to detect the anisotropic magnetic response of nanomaterials. Previously, we reported the chain-like assemblies of γ-Fe_2O_3 nanoparticles showed an anisotropic heating behavior in the presence of alternating magnetic field.[23] However, how to characterize the magnetic property of the assemblies in nanoscale remains a challenge. Here, we fabricated one assembled monolayer of γ-Fe_2O_3 nanoparticles fixed inside a hydrogel sheet onside the device by in situ polymerization. When a uniform magnetic field was exerted from two orthogonal directions, the chain-like assemblies of γ-Fe_2O_3 nanoparticles showed the significantly different EIS in two directions. This magnetic response of such small amounts of nanomaterials was hard to measure by the common equipment such as vibrating sample magnetometer. On the contrary, the disorganized nanoparticles showed the nearly identical EIS in two directions (Figure S10, Supporting Information). This case demonstrated this novel device may have promising potentials in nanoscaled characterization of magnetic property.

In summary, we fabricated a novel magnetosensor by using MagR/Cry4 complex as sensory component. Based on the magneto-perceptive mechanism, the magnetic field can cause the variation of molecular conformation so that the electrochemical impedance spectrum can reflect this information. This device realized the detection of 10 mT field and showed good linearity with the field intensity in range from 20 to 60 mT. We also found the light is necessary for the magnetic sensing with this device, partly proving the magneto–optical coupling mechanism of MagR/Cry4 complex in magnetic navigation. Moreover, it was demonstrated the natural proteins can be used as a magneto-sensor. Based on the fabrication technics, this device is facile to adapt to the flexible electronics. We believe this work will deepen understanding of the magnetosensing protein and bioelectronics, opening a door to exploit natural molecules as electronic components.

Experimental Section

Plasmids and Materials: Plasmids encoding His-tagged pigeon cryptochrome 4 (clCry4) and Strep-II tag MagR (clMagR) were provided by Xie's group, identical with those in ref. [13]. All the other chemicals in the experiments were purchased from Sigma Aldrich (USA).

Expression and Purification of Magnetic Protein: MagR protein and MagR/Cry4 complex can be prepared by expression and co-expression of clMagR and clMagR/clCry4 genes in *Escherichia coli* strain BL21 (DE3), respectively. The transfected bacteria were screened by resistance to ampicillin and Kanamycin. Then the selected bacteria were induced by 20 μM IPTG (isopropyl-D-1-thiogalactopyranoside) for 20 h at 15 °C to express the proteins. Thereafter, the bacteria were harvested and re-suspended in lysate buffer (pH = 8.0) which consisted of 20 mM Tris-HCl, 150 mM NaCl, 10 mM imidazole and one complete protease-inhibitor cocktail. Then the re-suspended cells were sonicated in ice bath and the soluble fraction was collected by centrifugation. The collected supernatant was loaded onto a pre-packed Ni-NTA agarose column. The proteins are eluted by buffer (pH 8.0, 20 mM Tris-HCl, 150 mM NaCl, and 300 mM imidazole) after full washing (pH 8.0, 20 mM Tris-HCl, 150 mM NaCl, and 20 mM imidazole). The proteins were then loaded onto a pre-packed Strep-Tactin column for further purification. The column was washed with the washing buffer (pH 8.0) consisting of 20 mM Tris-HCl, 150 mM NaCl to get the MagR/Cry complex. For preparation of MagR, after harvesting and lysing the bacteria, the supernatant was just loaded onto the Strep-Tactin column. The other processes were identical.

The eluted proteins can be condensed by ultrafiltration and transferred into phosphate buffer solution (PBS) using a Sephadex G-25 column (GE, USA). The final products were stored in 4 °C for further use. The purity was tested by electrophoresis of 10% SDS-PAGE.

The Fabrication of Microfluidic Chips: For the fabrication of the microfluidic chip, indium tin oxide (ITO) coated (thickness: ≈185 nm) glass substrate (34 × 26 × 1.1 mm^3) was used. ITO coating was patterned into a desired dimension by laser etching.

Sylgard 184 polydimethylsiloxane (PDMS) precursor and cross-linking catalyst (10:1 w/w) was mixed and degassed under vacuum. The mixture was spin-coated onto the polyimide film with a thickness of 80 μm and cured at 80 °C for 1 h. To make PDMS cuboid, the mixture was dropped into a flat dish with a thickness of 4 mm. After being cured at 80 °C, the PMDS sheet was manually cut into the cuboid with predesigned dimension (34 × 10 × 4 mm^3). The columnar inlet and outlet were also manually drilled and Ag/AgCl wire (diameter: 100 μm) can be inserted into the outlet as reference electrode (RE).

Then the PDMS film was cut according to the microfluidic channel pattern. After the ITO glass and channel PDMS film were treated by oxygen plasma for 5 min, they were bonded and placed in an oven at 80 °C for 2 h to enhance the bonding. There were two uncovered ITO areas in the channel. The wider one (2.8 mm × 10 mm) was used for further modification to serve as the working electrode (WE) and the other (0.8 mm × 10 mm) was directly used as the counter electrode (CE). After the modification of WE, a PDMS cuboid was bond to the channel PDMS to accomplish the microfluidic chip.

Modification of the Working Electrode: The WE was first coated by a layer of conductive silver paste on the ITO surface to enhance the conductivity. Then, one layer of reduced graphene oxide (rGO) was modified on the silver paste to further facilitate the transfer of electrons. The synthesis of rGO referred to refs. [24,25], which detailed steps were shown in Note S1, Supporting Information.

The abundant carboxyl groups on rGO layer were exploited to immobilize the proteins via EDC/Sulfo-NHS coupling reaction. The 80 mM EDC and 20 mM Sulfo-NHS were dissolved in 0.1 M 2-(4-morpholino) ethanesulfonic acid (PH 5.0). 50 μL of the mixed solution was dropped onto the surface of rGO electrode to activate the carboxyl groups. After 20 min, the rGO electrode was washed with PBS and dried with N_2 stream. Finally, 50 μL MagR/Cry4 complex (100 μg mL^{-1}) solution was dropped onto the surface of rGO electrode evenly and the chip was kept under 4 °C for incubation overnight. Then the modified WE was washed with PBS gently to remove the unbound proteins and dried with N_2 stream.

Measurement of Electrochemical Impedance: Impedance measurements were performed using a CHI660E Electrochemical Workstation (CH Instrument, USA). All the electrochemical measurements were carried out in 0.01 M PBS (pH7.4) containing 5 mM $K_4[Fe(CN)_6]/K_3[Fe(CN)_6]$ (1:1) at room temperature. The magnetic field was provided by a cuboidal permanent magnet which magnetic lines were parallel to the electrode plane. The measurement was carried out in an enclosed box which was fully coated with permalloy and copper mesh to shield the electromagnetic interference from environment. A small light-emitting diode flashlight was put inside the box to provide the light. The impedance measurements were conducted at equilibrium potential with 5 mV alternating voltage and the tested frequency was set from 100 kHz to 1 Hz. The measurement of one sample was repeated for at least three times.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

Acknowledgements

This work was financially supported by the National Key Projects for Research and Development Program of China (2017YFA0104301).

Conflict of Interest

The authors declare no conflict of interest.

Keywords

bioelectronics, magneto-sensing, MagR proteins, MagR/Cry4 complex

Received: October 22, 2019
Revised: February 16, 2020
Published online:

[1] H. Aceto, C. Tobias, I. Silver, *IEEE Trans. Magn.* **1970**, *6*, 368.
[2] J. Lenz, A. S. Edelstein, *IEEE Sens. J.* **2006**, *6*, 631.
[3] Y. G. Cornelissens, F. M. Peeters, *J. Appl. Phys.* **2002**, *92*, 2006.
[4] W. Wiltschko, R. Wiltschko, *J. Comp. Physiol., A* **2005**, *191*, 675.
[5] S. Zhan, C. Merlin, J. Boore, S. Reppert, *Cell* **2011**, *147*, 1171.
[6] C. Liang, C. Chuang, J. Jiang, E. Yang, *Sci. Rep.* **2016**, *6*, 23657.
[7] K. Maeda, K. B. Henbest, F. Cintolesi, I. Kuprov, C. T. Rodgers, P. A. Liddell, D. Gust, C. R. Timmel, P. J. Hore, *Nature* **2008**, *453*, 387.
[8] J. B. Phillips, M. Rachel, P. E. Jorge, *J. Exp. Biol.* **2010**, *213*, 3247.
[9] D. Immeln, A. Weigel, T. Kottke, J. L. P. Lustres, *J. Am. Chem. Soc.* **2012**, *134*, 12536.
[10] C. T. Rodgers, P. J. Hore, *Proc. Natl. Acad. Sci., U. S. A.* **2009**, *106*, 353.
[11] L. E. Foley, R. J. Gegear, S. M. Reppert, *Nat. Commun.* **2011**, *2*, 356.
[12] C. Bialas, L. E. Jarocha, K. B. Henbest, T. M. Zollitsch, G. Kodali, C. R. Timmel, S. R. Dutton, P. L. Mackenzie, C. C. Moser, P. J. Hore, *J. Am. Chem. Soc.* **2016**, *138*, 16584.
[13] S. Qin, H. Yin, C. Yang, Y. Dou, Z. Liu, P. Zhang, H. Yu, Y. Huang, J. Feng, J. Hao, J. Hao, L. Deng, X. Yan, X. Dong, Z. Zhao, T. Jiang, H. W. Wang, S. J. Luo, C. Xie, *Nat. Mater.* **2016**, *15*, 217.
[14] M. Jiang, L. Zhang, F. Wang, J. Zhang, G. Liu, B. Gao, D. Wei, *Sci. Rep.* **2017**, *7*, 13329.
[15] M. Meister, *eLife* **2016**, *5*, e17210.
[16] F. T. C. Moreira, R. A. F. Dutra, J. P. C. Noronha, J. C. S. Fernandes, M. G. F. Sales, *Sens. Actuators, B* **2013**, *182*, 733.
[17] Q. Liu, H. Wang, H. Li, J. Zhang, S. Zhuang, F. Zhang, K. J. Hsia, P. Wang, *Biosens. Bioelectron.* **2013**, *40*, 174.
[18] F. Lisdat, D. Schäfer, *Anal. Bioanal. Chem.* **2008**, *391*, 1555.
[19] W. Jie, P. Zoltan, M. A. Even, C. Zhan, *J. Am. Chem. Soc.* **2002**, *124*, 7016.
[20] Z. Chi, F. G. Wu, P. Hu, C. Zhan, *J. Phys. Chem. C* **2014**, *118*, 12195.
[21] I. F. Herbut, *Phys. Rev. B: Condens. Matter* **2006**, *75*, 1418.
[22] C. T. Lin, P. T. K. Loan, T. Y. Chen, K. K. Liu, C. H. Chen, K. H. Wei, L. J. Li, *Adv. Funct. Mater.* **2013**, *23*, 2301.
[23] K. Hu, J. Sun, Z. Guo, P. Wang, Q. Chen, M. Ma, N. Gu, *Adv. Mater.* **2015**, *27*, 2507.
[24] X. Zhang, Z. Sui, B. Xu, S. Yue, B. Liu, *J. Mater. Chem.* **2011**, *21*, 6494.
[25] Y. Xu, W. Hong, B. Hua, C. Li, G. Shi, *Carbon* **2009**, *47*, 3538.

