



Full paper

Piezotronically enhanced detection of protein kinases at ZnO micro/nanowire heterojunctions

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ABSTRACT

One-dimensional semiconductors can be combined with functional molecules to form planar van der Waals heterojunctions whose charge transport behavior is influenced by the heterojunction geometry, providing a new degree of freedom to engineer device functions. Here, we proposed a Schottky contacted single ZnO micro/nanowire sensor for detecting protein kinases activity in this paper. Protein kinases activity was investigated recur to the specific identification of ZnO to phosphorylated peptide and piezotronic effect on the performance of the phosphorylated peptide sensor with different compressive strain. The strain-induced piezoelectric polarization charges can adjust the Schottky barrier height, which can effectively enhance the overall performance of the designed device. Under the positive bias, the relative current changes at phosphorylated peptide concentrations of 10 nM enhanced from 3% to 66%, respectively, as the applied compressive strain increased from 0.00% to 0.72%. This work provides a promising piezotronically enhanced Schottky contacted single ZnO micro/nanowire-based protein kinases sensor. A detailed understanding of how the electrostatics affect charge transport in nanowire/molecule heterojunctions inform the design of future van der Waals heterojunction detectors and transistors, which is relevant in the design of nanowire applications.

1. Introduction

Protein kinases (PKs) play critical regulatory roles in most signal transduction pathways respect to various cellular functions [1,2]. PKs could catalyze peptide/protein substrate to be phosphorylated by transferring phosphoryl group to the special amino acid in the substrate. Aberrant activity of PKs is closely related to many human diseases, such as cancer, diabetes and so on [3,4]. Since the activity of the PKs can

serve as indicatives for many diseases, developing sensitive detection methods has become a critical issue for PKs-targeted drug screening, clinical diagnosis and fundamental research. So far, there are so many methods developed for detecting PKs, such as radioactive methods, antibody methods, fluorescence, electrochemical technologies and so on [5–9]. Although these assays provide great advances for detecting PKs, most of them need either especial decoration, or expensive instruments. In consideration of the special complex decoration, developing

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label-free detection method which can offer facile, low-cost, and sensitive strategy for detecting the activity of PKs is still imperative.

Recently, semiconducting one-dimensional nanostructures such as nanorods, nanowires and nanobelts have drawn much attention for their unique properties [10–12]. The sensor devices based on semiconductor nanomaterials provide label-free direct detection through the electrical readout of the devices for sensing various chemical and biological molecules. The nanowire devices based on field effect transistors have been extensively used in various fields of energy sciences, electronics, and sensors [13–17]. The nanowires are good candidates for sensing diverse chemical and biological molecules by direct detecting electrical readout without extra modification. The Ohmic contacted field effect transistors detection depends on the change of resistance before and after being adsorbed on the nanowire surface [18]. Although lots of sensors based on Ohmic contacted have been developed to improve the output signals and sensitivity, there is a big challenge for that to fabricate small size nanowire sensors are complex and difficult, and the Ohmic contacted device has low sensitivity. In contrast, Schottky contacted nanowire sensors exhibit much more sensitivity, and have been fabricated for sensing gas, pH, glucose and so on [14,15,19–21]. The sensitivity performance of the sensor relies on the optimum of Schottky barrier height (SBH) across the metal-semiconductor (M – S) interface [14,17].

On account of the non-central symmetric crystal structure of the wurtzite/zinc semiconductor materials, piezoelectric potential is created in materials by applying external strains [22]. The piezoelectric polarization charges created inside the wurtzite structured nanowire are the origin of the piezotronic effect and can be used to tune the SBH effectively across the interface or junction region, which could affect the charge transport properties [23]. Devices based on wurtzite structured semiconductor nanowires have been verified that piezotronic effect could largely improve the detection sensitivity, and it has excellent performance by simply applying strain to the device [14,15,24]. Thus we proposed a single ZnO micro/nanowire heterojunctions based method to detect the activity of PKs. In recently, a variety of assays for activity of PKs have been reported. In 2016, Qi's group achieved the detection to the activity of PKs by ruthenium derivative-labeled probe via gold electrode, which is high cost [25]. In addition, Yan and co-workers assembled DNA conjugated gold nanoparticles to phosphorylated kemptide modified TiO_2/ITO electrode to study the activity of PKs in 2015, which needs tedious material preparation process [26]. The most common approaches to PKs activity is radioactivity-based assay where phosphoryl transfer from $[\gamma\text{-}^{32}\text{P}]\text{ATP}$ to a peptide or protein substrate is quantified by scintillation counting. This method not only requires special handling but also generate radioactive waste [2]. In this work, 10 nM of phosphorylated peptide could be detected, and the relative current change enhances from 3% to 66%, as the applied compressive strain increases from 0 to 0.72% respectively. What's more, piezotronically enhanced detection of PKs at ZnO micro/nanowire heterojunctions is proposed firstly, which is sensitive and in situ selective label-free sensor that can be easily fabricated.

In this paper, we proposed a sensitive and label-free PKs sensor based on a single ZnO micro/nanowire. The PKs detection was realized via piezotronic effect based sensor with Schottky contacted structure. Piezotronic effect is introduced by exerting external strains on the ZnO micro/nanowire sensor to improve the performance and sensitivity. The results indicate that the relative output current signal is significantly enhanced by 73% when the 0.72% compressive strain is applied on the Schottky contacted single ZnO micro/nanowire-based sensor. Under 0.00% compressive stress, the relative current change of 10 nM phosphorylated peptide is 3%, and the relative current change of 10 μM phosphorylated peptide is 81%. Furthermore, under 0.72% compressive stress, the relative current change increase from 66% to 94% when the phosphorylated peptide concentration increase from 10 nM to 10 μM . In the ZnO micro/nanowire sensor device, piezo-polarization charge induced by external strain plays an important role in process of the

modification of the band structure at M – S contact and the charge carrier transport across the Schottky barrier. This proposed design provides a foreground detection method for PKs based on Schottky contacted ZnO micro/nanowire.

2. Results and discussion

The principle schematic of the proposed strategy of the ZnO micro/nanowire sensor for PKs is shown in Fig. 1a. PKs act as the catalyst to make protein to be phosphorylated, and the special amino acid site is introduced the phosphoric acid group. The single ZnO micro/nanowire is used to screening the phosphorylated peptide in the PKs reaction solution through adsorption effect and reaction. In the absence of PKs, the peptide is still nonphosphorylated and there is no phosphate group in the peptide. When the PKs reaction solution is dropped on the surface of the device, nonphosphorylated peptide and phosphorylated peptide are distinguished by ZnO micro/nanowire. The phosphorylated peptides could bond to ZnO micro/nanowire in the incubation process of ZnO micro/nanowire and PKs solution. Upon the bonded phosphorylated peptide, the piezotronic effect of ZnO micro/nanowire was changed significantly compared to unmodified ZnO micro/nanowire. So the activity of the PKs can be directly reflected by detecting the piezotronic signal of single ZnO micro/nanowire sensing system under different external strains.

Fig. 1b and c shows the digital image and optical microscopy image of single ZnO micro/nanowire device sensor for PKs. The ZnO micro/nanowire used in this assay was synthesized via vapor-solid process according to previous works [12,27]. The synthesized ZnO micro/nanowires were characterized by scanning electron microscopy (SEM) as shown in Fig. 1e and f. The length of the ZnO micro/nanowires are extremely long with lengths of several hundreds of micrometers and even to several millimeters, and the diameters vary from tens of nanometers to several micrometers. Fig. 1d is the schematic diagram of the three-dimension mechanical stage with the motion resolution of 1 μm . This experimental setup was used to detect the piezotronic effect of the proposed PKs sensor by fixing one end of the device on the setup and applying external strains on the other free end of the device. The response of the ZnO micro/nanowire sensor to PKs is evaluated by measuring its output currents under different strains at the bias voltage ranging from -1.5 V to $+1.5$ V.

In order to prove the feasibility of the proposed ZnO micro/nanowire sensor for PKs, the protein tyrosine kinase Src-specific peptide labeled by fluorescence TAMRA-IYGEFCK, and its phosphorylated counterpart TAMRA-I (pY)GEFCK were used. The TAMRA is a fluorescent dye that exists strong fluorescence at 583 nm under the optimal excitation wavelength of 554 nm [8]. After being incubated with phosphorylated and nonphosphorylated peptide respectively, the fluorescence intensities of ZnO micro/nanowire sensors were recorded by laser scanning confocal microscopy under the excitation laser of 543 nm. As shown in Fig. 2, the ZnO micro/nanowire sensor incubated with phosphorylated peptide exhibits high fluorescence intensity. On the contrary, the fluorescence signal of the ZnO sensor is still weak after incubation with nonphosphorylated peptide. These results clearly illustrate that the phosphorylated peptide could strongly bond with ZnO micro/nanowire and be successfully adsorbed on ZnO micro/nanowire surface. Therefore, the activity of PKs can be simply detected by incubating the PKs reaction solution with single ZnO micro/nanowire sensor, which could be detected by monitoring the piezotronic effect signal of the ZnO micro/nanowire sensor.

To detect the activity of PKs based on the proposed single ZnO micro/nanowire sensor, different concentrations of phosphorylated peptide solutions were investigated through measuring its output currents under different strains at the bias voltage ranging from -1.5 V to $+1.5$ V. Fig. 3 shows the I–V response of the ZnO micro/nanowire device incubated with different concentration of phosphorylated peptide under varying external strain. The experiments were carried out by applying

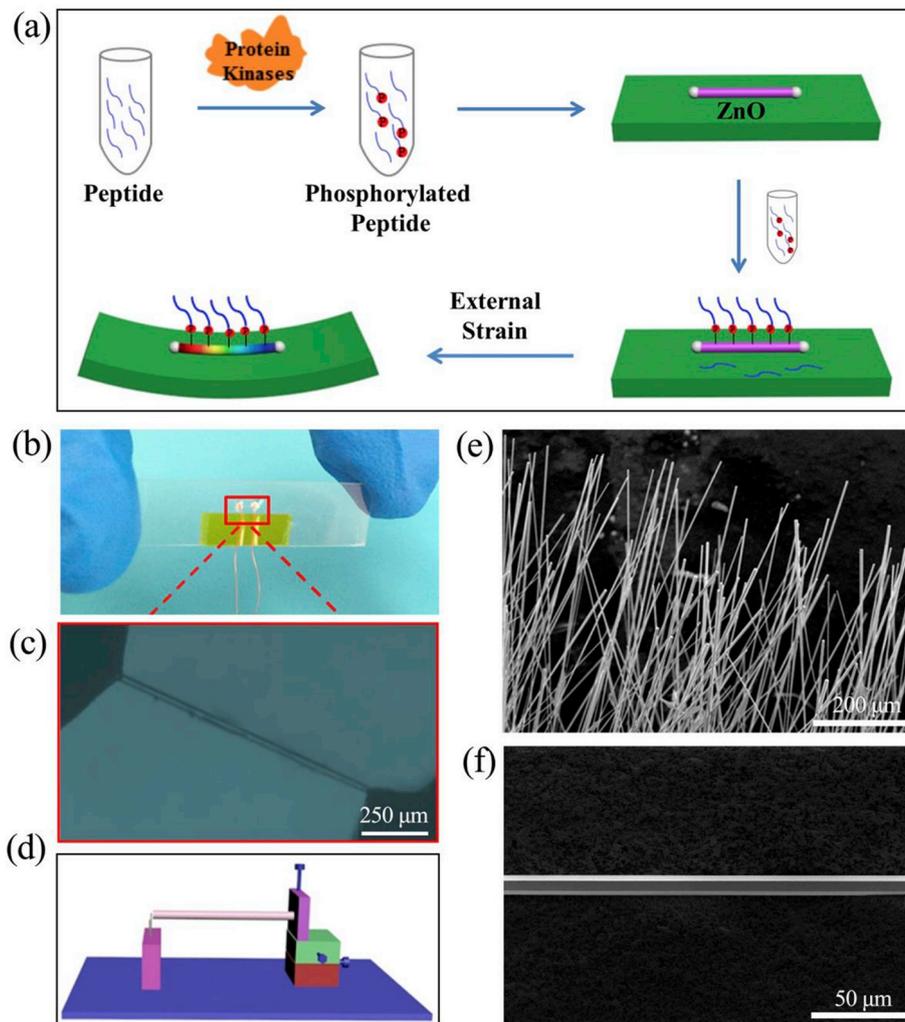


Fig. 1. (a) Schematic illustration of the detection process based on ZnO micro/nanowire sensors for detecting the protein kinases. Digital image (b) and optical microscopy image (c) of the ZnO micro/nanowire sensor. (d) Schematic illustration of the experimental equipment three-dimensional mechanical stage. (e) SEM image of the synthesized ZnO micro/nanowire. (f) High-magnification image of single ZnO micro/nanowire.

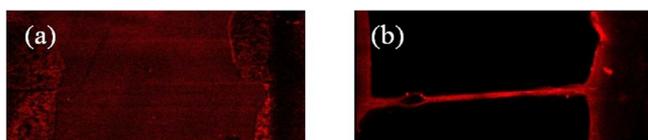


Fig. 2. Laser scanning confocal microscopy images of the ZnO micro/nanowire sensor after reacting with (a) nonphosphorylated peptide and (b) the corresponding phosphorylated peptide under the excitation of 543 nm laser.

different external strain from 0.00% to 0.72% at fixed concentration of phosphorylated peptide. The current decreases obviously when increase the applied external strain ranging from 0.00%, 0.18%, 0.36%, 0.54%–0.72%. As shown in Fig. 3a, at the fixed phosphorylated peptide concentration of 10 nM, the current performance of the sensor drops from 2.50 μA to 0.71 μA (by 1.79 μA) when the compressive strain increases from 0.00% to 0.72%. Under the same strain condition, the current drops from 0.49 μA to 0.13 μA (by 0.36 μA) when the concentration is 10 μM shown in Fig. 3d. The decrease of sensor current is about 80% as the concentration increasing from 10 nM to 10 μM . The I–V curves were nonsymmetrical and nonlinear indicating that the SBH at the two contacts are different. The behave of this device looks like two back-to-back connected diodes. Under bias voltage, the electrical transport property is mainly controlled by the reversely Schottky barrier [14,17]. These

results confirm that the single ZnO micro/nanowire has good response to PKs by incubating the ZnO micro/nanowire with PKs reaction solution, and the sensitivity of the sensor can be largely improved by the piezotronic effect after applying external strains.

Parts a and b of Fig. 4 show the piezotronic performance of the ZnO micro/nanowire sensor for PKs under 0.18% and 0.54% compressive strain respectively with the concentration of phosphorylated peptide varying from 10 nM (0.01 μM) to 10 μM . The current of the sensor drops conspicuously with the increase of the concentration of phosphorylated peptide. Fig. 4a shows the current drops from 2.04 μA to 0.43 μA under 0.18% strain when the concentration increases from 10 nM to 10 μM . The current variation is 1.61 μA when the strain is 0.18%, while the variation is 0.76 μA decreasing 53% as the strain increases to 0.54% shown in Fig. 4b. The results confirm that the ZnO micro/nanowire sensor exhibits good sensitivity for lower concentration of phosphorylated peptide, and prove once more that piezotronic effect is closely related to the current performance of the sensor.

To investigate the specificity of the proposed ZnO micro/nanowire PKs sensor for the phosphorylated peptide, nonphosphorylated peptide with different concentration has been investigated under the same conditions. The ZnO micro/nanowire sensor was measured under 0.00% strain after being incubated with different concentrations of non-phosphorylated peptide ranging from 10 nM to 10 μM . It can be seen from Fig. 4c, with the concentration increase from 10 nM to 10 μM , the

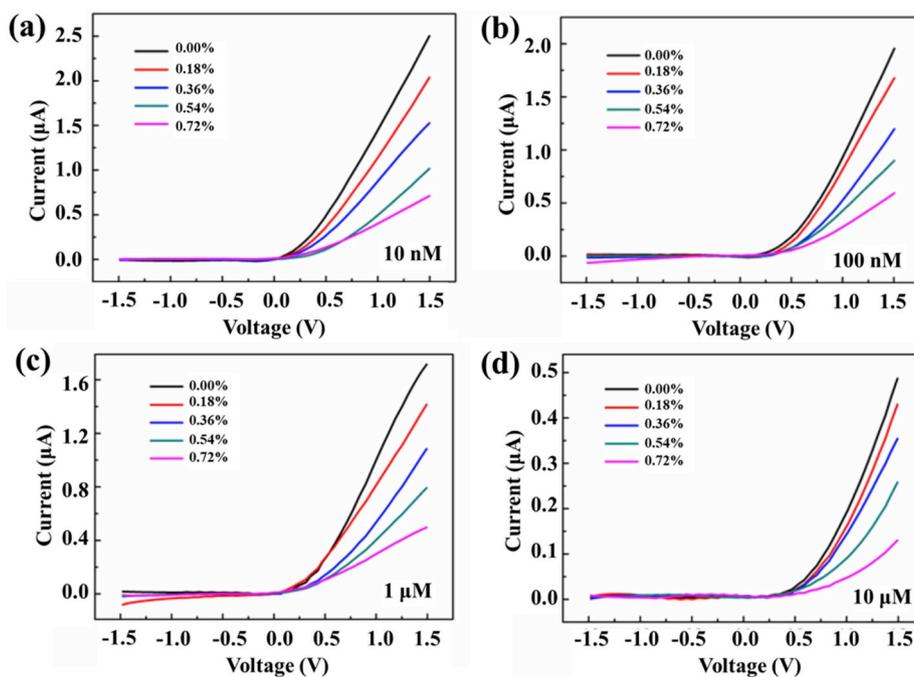


Fig. 3. I–V curves of the ZnO micro/nanowire protein kinase sensor under different compressive strains, when the sensor was incubated with (a) 10 nM, (b) 100 nM, (c) 1 μM and (d) 10 μM phosphorylated peptide.

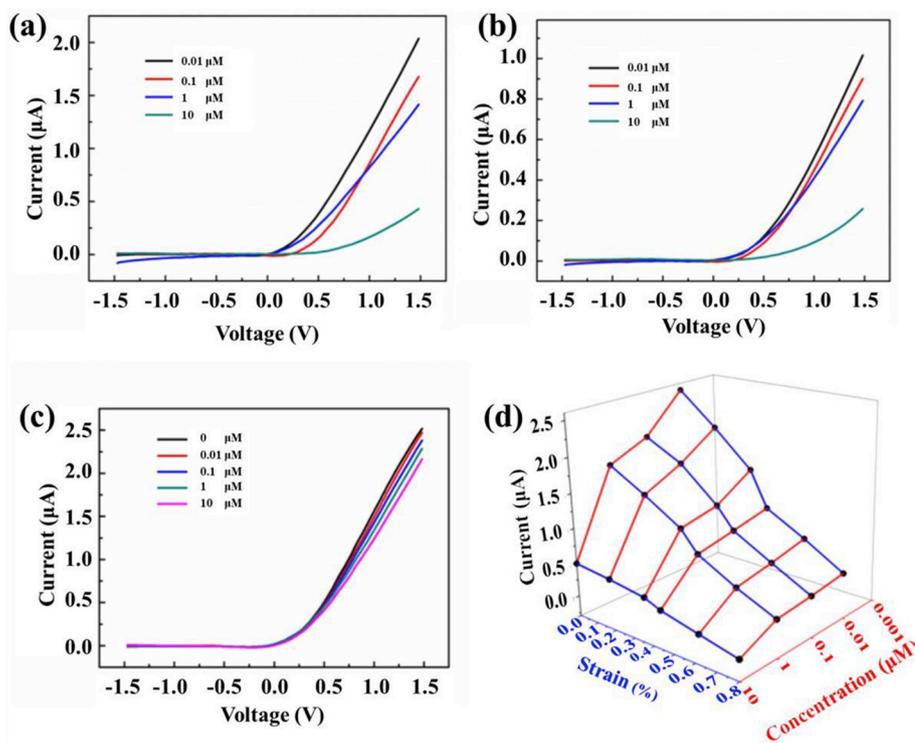


Fig. 4. I–V curves of the ZnO micro/nanowire sensor under 0.18% (a) and 0.54% (b) compressive strain. (c) I–V curves of ZnO micro/nanowire sensor was measured under 0.00% strain after being incubated with different concentrations of non-phosphorylated peptide ranging from 10 nM to 10 μM. (d) 3D graph depicting the current response of the ZnO micro/nanowire protein kinase sensor to different strains and varying concentrations of phosphorylated peptide under a bias voltage of 1.5 V.

current of the sensor drops slightly from 2.47 μA to 2.17 μA (by 12%). However, the current drops from 2.50 μA to 0.49 μA (by 80%) for the phosphorylated peptide at the same condition (Fig. 4d). Compared to phosphorylated peptide, the amplitude of current variation of non-phosphorylated peptide is negligible. The result indicates that specificity of the ZnO micro/nanowire PKs sensor is excellent for PKs analysis.

To systematically analyze the ZnO micro/nanowire PKs sensor response to constantly changing compressive strains and target

phosphorylated peptide concentration, a three-dimensional (3D) graph was plotted, as depicted in Fig. 4d. As presented, the output current decreases obviously with the increase of the concentration of phosphorylated peptide or compressive strains. The detailed absolute and relative current changes of the sensor are shown in Fig. 5a–d.

Fig. 5a and b shows the absolute and relative current change of ZnO micro/nanowire sensor, which were measured in different concentrations (0, 10 nM, 100 nM, 1 μM and 10 μM) at the fixed compressive

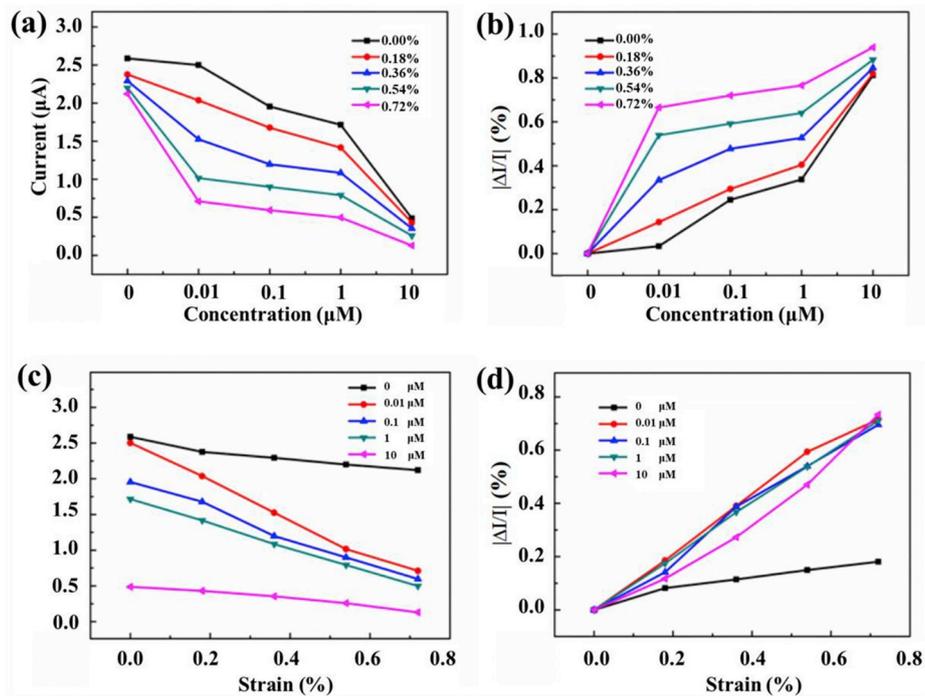


Fig. 5. Piezotronic performances of the ZnO micro/nanowire Sensor. (a, b) Absolute and relative current response to different phosphorylated peptide concentration, with compressive strains ranging from 0.00% to 0.72%. (c, d) Absolute and relative current response of the ZnO micro/nanowire sensor under different compressive strain, with phosphorylated peptide concentration ranging from 0 μM to 10 μM .

strain. The five curves shown in Fig. 5a have the same trend, which illustrates that the output current decreases with the increase of the phosphorylated peptide concentration at the fixed external compressive strain. For example, at the 0.00% external strain, the current decreases from 2.58 μA to 0.88 μA (by 66%) with increasing the concentration of phosphorylated peptide from 0 to 10 μM . The result indicates that the proposed single ZnO micro/nanowire sensor is excellent for sensing PKs

at different external strains. The corresponding relative current change of the PKs sensor shown in Fig. 5b illustrates that the piezotronic effect has a great effect on the detect sensitivity. For the concentration of 10 nM, the relative current variable is 3% at the 0.00% compressive strain, at the same time it is 66% at the 0.72% compressive strain which is 22 times larger than no strain. The result indicates that the larger external strains applying to the device, the lower concentration of

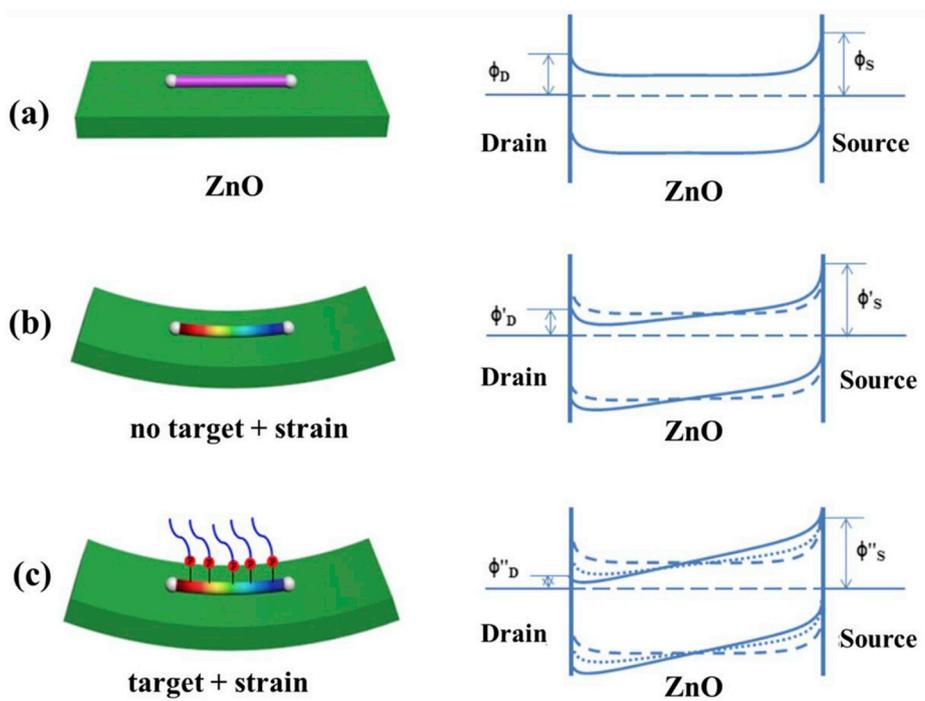


Fig. 6. Piezotronic performance schematic diagrams of the ZnO micro/nanowire protein kinase sensor under different conditions: (a) unstrained, (b) compressively strained without the target, (c) compressively strained with the target phosphorylated peptide.

phosphorylated peptide would be detected. The piezotronic effect could obviously improve the detection sensitivity of the proposed ZnO sensor.

Fig. 5c and d shows the absolute and relative current response of PKs sensor to varying strains, with the concentration of peptide from 0 to 10 μM fixed for each line. The absolute output current of the sensor decreases with the increase of compressive strain at the fixed concentration. The results further indicate that the piezoelectric effect has an important influence on the proposed single ZnO micro/nanowire sensor for PKs.

In order to investigate the enhanced performance of the ZnO micro/nanowire sensor for PKs by piezotronic effect, the theoretical energy band model was shown in Fig. 6. And Fig. 6a shows the energy band diagram of single ZnO micro/nanowire sensor out of strain. The two ends fixed by silver construct a metal-semiconductor-metal (M-S-M) structure, and the height of the SBH at each M – S contact is different. The transport property of the ZnO micro/nanowire sensor is dominantly controlled only by the reversely biased Schottky junction/barrier, i.e. the Schottky barrier of the drain electrode Φ_d [14,28]. Fig. 6b shows the change of sensor energy band with no target under compressive strain. When the compressive strain was applied to the ZnO micro/nanowire, piezoelectric potential was created inside the ZnO micro/nanowire along the c-axis. Due to the piezo-charges were introduced to the drain electrode and source electrode, the SBH variation of each electrode changes differently. The positive piezoelectric polarization charges induced to the M – S contact of drain electrode would reduce the SBH and lead to the increase of current.

In this proposed design, ZnO micro/nanowire acts as the recognition to distinguish the phosphorylated and nonphosphorylated peptide. In the presence of PKs, the substrate peptide was catalyzed and the specific amine acid site in the peptide was introduced into the phosphor group. In a fixed concentration of peptide substrate, the higher activity of PKs, the more peptides were phosphorylated. The phosphorylated peptide could be absorbed and immobilized on the surface of ZnO micro/nanowire may due to existing phosphate groups and Zn^{2+} ions. When introduced the PKs reaction solution onto the ZnO micro/nanowire, the phosphorylated peptides would quickly bonded to the ZnO micro/nanowire. However, the nonphosphorylated peptides were bonded weakly and free. In consideration of that the difference of phosphorylated and nonphosphorylated peptide for the ZnO micro/nanowire, the PKs sensor based on single ZnO micro/nanowire has been developed. As shown in Fig. 6c, the phosphorylated peptide was absorbed on the surface of the ZnO micro/nanowire leading to changes of SBH of each electrode and output current. Upon introducing phosphorylated target into the ZnO micro/nanowire, phosphor group would interact with the oxygen vacancies or zinc interstitial, and become negatively charged unit by acquiring electrons from ZnO [28]. This leads to the decrease of free electrons inside of ZnO and the decrease of output current of the ZnO sensor. In conclusion, the single ZnO micro/nanowire could be utilized to sensor PKs by detecting piezotronic effect upon applying strains on the device.

3. Conclusion

In summary, a Schottky contacted single ZnO micro/nanowire sensor is developed for the sensitive detection of PKs activity. The proposed design is based on the difference of ZnO bonding force towards unphosphorylated peptide and phosphorylated peptide which are products before and after PKs reaction respectively. Phosphorylation of the peptide provides a way to bound on the surface of ZnO micro/nanowire and significantly improve the piezotronic effect. The performance of the ZnO micro/nanowire sensor for PKs was investigated by detecting current under a series of compressive strains after reacting with varying concentrations of phosphorylated peptide. By employing a series of compressive strains, the highly sensitive performance of the ZnO sensor was achieved due to the piezotronic effect. This proposed method is highly sensitive in the range of 10 nM to 10 μM . The relative

current variable of 10 nM phosphorylated peptide at the 0.72% compressive strain is 22 times larger than no strain. The theoretical energy band model of the ZnO sensor is presented to illustrate the performance under different conditions. The piezotronic effect could change the SBH and effectively improve its sensitivity and the lowest detectable concentration is 10 nM. Therefore, this novel strategy based on the piezotronic effect of single ZnO micro/nanowire provides a promising platform for detecting PKs.

4. Experimental section

4.1. Reagents

The peptides including TAMRA-IYGEFCK, TAMRA-I (pY)GEFCK, IYGEFCK and I (pY)GEFCK were synthesized by GL Biochem Ltd. (Shanghai, China). The Tris buffer (0.5 M, pH 6.8) was supplied by Sangon Biotech. All other reagents used in this assay were analytical grade and used without any further purification.

4.2. Synthesis of ZnO micro/nanowire

The synthesis of ZnO micro/nanowire was performed through a vapor-solid (VS) growth method referring to previous work [12,27]. 1 g of ZnO nanopowder and 1 g of activated carbon powder were ground well and mixed uniformly. Then the mixed materials were transferred to an alumina boat, and the silicon substrate with a 2 nm gold catalyst layer facing down was horizontally put on top of the boat. The synthesis temperature was kept at 1000 °C with the flow rate of argon gas at 100 standard cubic centimeters per minute for 1 h. When the furnace was cooled down to room temperature, the product could be collected for further use.

4.3. Fabrication of PKs sensor

The PKs sensors were fabricated by transferring a signal ZnO micro/nanowire onto a flexible polyethylene terephthalate substrate. Silver conductive adhesive, served as electrode, was used to fix the two ends of signal ZnO micro/nanowire. After that, epoxy adhesive was spread on the silver electrodes for avoiding the interference of the reaction solution to the electrodes. Typically, a 5 μL of phosphorylated peptide solution with certain concentration was incubated with ZnO micro/nanowire at 37 °C for 30 min. After the reaction, the device was washed by buffer solution for three times to remove the uncombined and weak binding peptide. In the process of detection, one end of the device was immobilized on the holder, and the other end was flexible to be bent by the shaft of the three-axis translation stages with the resolution of 1 μm . The strain can be calculated according to Yong et al.'s published work [29]. The PKs sensor based on the ZnO micro/nanowire was obtained.

Declaration of competing interest

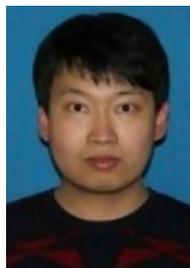
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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