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Highly sensitive detection of urinary protein variations using tilted fiber grating sensors with plasmonic nanocoatings

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ABSTRACT

Surface plasmon resonance (SPR) optical fiber biosensors can be used as a cost-effective and relatively simple-to-implement alternative to well established bulky prism configurations for high sensitivity biological sample measurements. The miniaturized size and remote operation ability offer them a multitude of opportunities for single-point sensing in hard-to-reach spaces, even possibly in vivo. The biosensor configuration reported in this work uses a tilted fiber Bragg grating (TFBG) in a commercial single mode fiber coated with a nanometer scale silver film. The key point is that by reducing the silver film thickness to around 20–30 nm (rather than 50 nm for optimal SPR excitation), different modes of the TFBG spectrum present very high but opposite sensitivities to refractive index (RI) changes around the TFBG. Experimental results obtained with the coated TFBG embedded inside a microfluidic channel show an amplitude sensitivity greater than 8000 dB/RIU (Refractive Index Unit) and a limit of detection of 10^{-5} RIU. Using this device, the effect of different concentrations of protein in rat urine was clearly differentiated between healthy samples, nephropatic samples and samples from individuals under treatment, with a protein concentration sensitivity of 5.5 dB/(mg/ml) and a limit of detection of 1.5×10^{-3} mg/ml. Those results show a clear relationship between protein outflow and variations in the RI of the urine samples between 1.3400 and 1.3408, pointing the way to the evaluation and development of new drugs for nephropathy treatments. The integration of TFBGs with microfluidic channels enables precise measurement control over samples with sub-microliter volumes and does not require accurate temperature control because of the elimination of the temperature cross-sensitivity inherent in TFBG devices. Integration of the TFBG with a hypodermic needle on the other hand would allow similar measurements in vivo. The proposed optical fiber/microfluidic plasmonic biosensor represents an appealing solution for rapid, low consumption and highly sensitive detection of analytes at low concentrations in medicine as well as in chemical and environmental monitoring.

1. Introduction

Human urine normally contains a few volume of protein that is less than 150 mg per 24 h and it is hard to be identified by routine tests. Proteinuria, defined as urinary protein excretion greater than 300 mg per 24 h, is an important sign for renal damage and its expression often precedes any detectable decline in renal filtration function. The increase of proteinuria accelerates kidney damage and promotes the progression of chronic kidney disease (CKD) and finally leads to end-stage renal disease (ESRD) (Ishani et al., 2006; Tonelli et al., 2011). Previous studies identify that proteinuria is a strong and independent predictor of the increased risk for cardiovascular mortality in CKD patients with or without diabetes (Agrawal et al., 2009; Matsushita et al., 2010). Therefore, early diagnosis of proteinuria is essentially important for prevention and treatment of chronic kidney disease and its complications. Traditional methods to identify the small changes in urine due to expression increasing of protein are conducted by detecting the protein excretion. The most widely accepted formats of “wet-lab” type analytic biochemistry assays are the Coomassie brilliant blue protein assay (Chial et al., 1993) and the bicinchoninic acid assay

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(BCA) (Smith et al., 1985). These methods are commonly implemented using bulk optic laboratory instrumentation (like microplate array systems) in applications such as pharmaceutical research where a large number of tests performed simultaneously in parallel. However these methods are susceptible to environmental interferences and suffer from time consuming sample preparation (having to bring samples back to a laboratory and label the sample for additional selection and amplification). Designing new sensing techniques with detection levels and reliability comparable to large laboratory instruments, but using label-free methods in small scale point-of-care devices is an important development in this field.

The use of optical fiber devices as biomedical sensors presents many well-known desirable features (size, cost, feasibility) for label-free methods as they contribute to the overall reduction in costs and ease of use factors (Baldini et al., 2012; Wang and Wolfbeis, 2013). Fiber optic sensors can be easily inserted into the media to be sensed (instead of having to bring samples inside an instrument) either as a hand held probe or as a set of remotely operated devices along a fiber optic cable (in environmental monitoring applications for instance). However, it should be noted that for biochemical sensing fields, it is usually necessary to improve the limit of detection (LOD) levels to at least 10^{-5} RIU (Refractive Index Unit), by increasing the wavelength shift sensitivity while keeping noise level down and spectral features narrow (White and Fan, 2008). Fortunately, it has been recently demonstrated that the addition of a nanometric-scale gold or silver coating overlay on the optical fiber outer surface considerably enhances the refractometric sensitivity through the generation of surface plasmon resonance (SPR) (Homola, 2008; Piliarik and Homola, 2009; Shalabney and Abdulhalim, 2011; Caucheteur et al., 2015). The increased sensitivity achieved with plasmon waves arises because of the large localization of electromagnetic energy in the layer immediately adjacent to the metal surface. Any perturbation in that layer, such as the bonding of analytes on receptor molecules modifies the local refractive index (RI) of the dielectric and the plasmon phase velocity. Meanwhile, in order to effectively excite and accurately measure plasmon resonances and hence to achieve this optimum sensitivity, a new kind of fiber grating, i.e. the tilted fiber Bragg grating (TFBG, corresponds to a RI modulation angled by a few degrees relative to the perpendicular to the propagation axis) has been developed and well studied (Albert et al., 2013; Guo et al., 2014, 2016; Thomas et al., 2012; Caucheteur et al., 2013). TFBGs benefit from two unique features: the strong polarization selectivity of the excited cladding modes (coming from the breaking of the cylindrical symmetry of non-polarization-maintaining fibers) and the high-density comb of narrowband spectral resonances (available to excite SPR over a wide range of refractive indices and to measure their spectral location with quality factors between 10^3 and 10^4). Therefore, SPR based TFBG sensors open up a multitude of opportunities for single-point biomedical sensing in hard-to-reach spaces, and offer an extremely improved LOD level to molecular interactions together with very controllable cross-sensitivities (Voisin et al., 2014; Lepinay et al., 2014; Shevchenko et al., 2014).

It is the purpose of this paper to demonstrate the intrinsic relationship between protein outflow (induced by adriamycin nephropathy) and RI variation (over the range of 1.3400–1.3408 approximately) in urine by simply using an in-fiber based, label-free direct detection device. This particular TFBG configuration has been optimized with an especially designed metal coating that allows both SPR excitation and conventional evanescent field probing of the medium refractive index, thereby enabling a novel differential data analysis method which increases the protein concentration sensitivity of 5.5 dB/(mg/ml) and a limit of detection of 1.5×10^{-3} mg/ml over repeated measurement of rat urinary samples with different concentration of protein. The detection process was precisely controlled with a micro-fluidic chip which allows the measurement of μL-volumes of bio-sample solutions. The proposed in-fiber plasmonic biosensor shows a minimal cross-sensitivity to temperature (through referencing of the spectrum by the core mode resonance) and its fabrication (UV-light grating-inscription and surface nanometric-coating) does not impact the structural integrity of the fiber so as to ensure the sensing stability and reproducibility. Finally, our study on the relationship between the outflow of protein and RI variation in urine will be helpful to the understanding and evaluation of adriamycin nephropathy (Okuda et al., 1986; Jeyaseelan et al., 2006).

2. Materials and methods

2.1. Bio-samples preparation

The schematic of the pharmacological process of adriamycin nephropathy and of the urine detection with a fiber-optic sensor

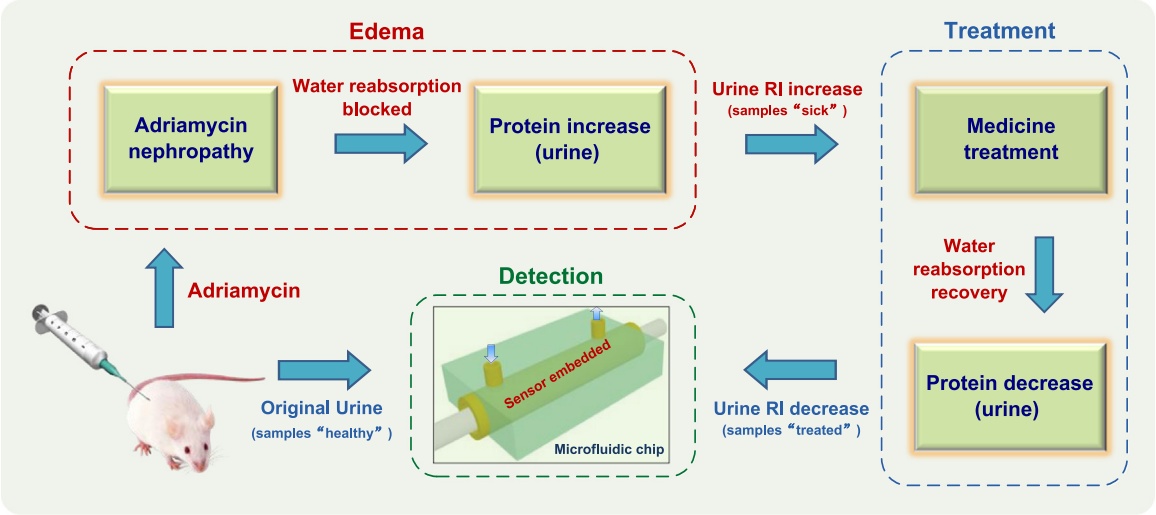

Fig. 1. Schematic of the pharmacological process of adriamycin nephropathy and of the urine detection with a fiber-optic sensor embedded in a microfluidic chip.