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Short communication

Electrochemical detection of β-amyloid peptides on electrode covered with N-terminus-specific antibody based on electrocatalytic O_2 reduction by Aβ(1–16)-heme-modified gold nanoparticles

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ABSTRACT

β-Amyloid (Aβ) peptides are believed to be important for the diagnosis and prognosis of Alzheimer's disease (AD) serving as reliable molecular biomarkers. In this work, we reported a simple and sensitive electrochemical strategy for the detection of total Aβ peptides using gold nanoparticles modified with Aβ (1–16)-heme (denoted as Aβ(1–16)-heme-AuNPs). Monoclonal antibody (mAb) specific to the common N-terminus of Aβ was immobilized onto gold electrode for the capture of Aβ(1–16)-heme-AuNPs. The anchored Aβ(1–16)-heme-AuNPs showed strong electrocatalytic O_2 reduction. Pre-incubation of the mAb-covered electrode with native Aβ decreased the amount of Aβ(1–16)-heme-AuNPs immobilized onto the electrode, resulting in the decrease of the reduction current of O_2 to H_2O_2. The competitive assay is sensitive and selective to Aβ peptides. The voltammetric responses were found to be proportional to the concentrations of Aβ ranging from 0.02 to 1.50 nM, and a detection limit of 10 pM was achieved. To demonstrate the viability of the method for the analysis of Aβ in real sample, artificial cerebrospinal fluid (aCSF) containing Aβ(1–40), Aβ(1–42) and Aβ(1–16) was tested. We believe that the method would offer a useful means for quantifying Aβ in a biological matrix, and be valuable in the design of new types of electrochemical biosensors for the detection of peptides and proteins.

1. Introduction

Alzheimer's disease (AD) is the most common chronic and progressive form of neurodegenerative disease, which is predicted to affect 1 in 85 people globally by 2050 (Brookmeyer et al., 2007). One of the pathological hallmarks of AD is the deposition of β-amyloid (Aβ) peptides including 39–42 amino acid residues in the brain (Rauk, 2009; Rolinski et al., 2010). In its native form, Aβ is unfolded but aggregates into a β-sheet structure of ordered fibrils under various conditions. Among kinds of the Aβ species (e.g., Aβ (1–28), Aβ(1–33), Aβ(1–34), Aβ(1–37), Aβ(1–38), Aβ(1–39), Aβ(1–40) and Aβ(1–42)) in human cerebrospinal fluid (CSF), Aβ(1–40) (60–70%) and Aβ(1–42) (5–15%) are the two predominant proteolytic cleavage products from amyloid precursor protein (APP) by β- and γ-secretase (Golde et al., 2000). The principal species deposited within the parenchyma of the AD brain is Aβ(1–42), which exhibits greater tendency to form amyloid fibrils than Aβ(1–40) (Beeg et al., 2011; Ogi et al., 2013). Aβ monomer and its aggregates are therefore considered as promising biomarkers for AD in spite of their controversial role in AD pathogenesis (Ammar et al., 2013; Choi et al., 2011; Doong et al., 2010; Golde et al., 2000; Haes et al., 2005). To date, a few attempts including mass spectrometry (Wang et al., 1996), enzyme-linked immunosorbent assay (ELISA) (Gravina et al., 1995), capillary electrophoresis (Picou et al., 2010) and surface plasmon resonance (SPR) (Ryu et al., 2008; Xia et al., 2010) have been made to detect Aβ species. However, most of these methods are expensive, time-consuming, labor intensive and/or less sensitive (Kang et al., 2009; Mustafa et al., 2010; Stravalaci et al., 2011). Thus, simple, cost-effective and sensitive method for Aβ detection has important clinical implication.

In recent years, electrochemical biosensors have found wide applications in clinical diagnosis, biomedical research, food quality control and environmental monitoring in view of its high sensitivity, simplicity, rapid response, and compatibility with miniaturization. There have also been some attempts for probing of Aβ aggregation and its interaction with biomolecules, drugs and metal by electrochemical techniques (Chikae et al., 2008; Grabowska et al., 2010; Islam et al., 2011; Jiang et al., 2010; Liu et al., 2011; Partovi-Nia et al., 2012; Pramanik et al., 2012; Szymánska et al., 2007; Vestergaard et al., 2005). For example, Vestergaard et al. (2005) presented the kinetic study of Aβ

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aggregation by the electrochemical oxidation of tyrosine (Tyr) residue in Aβ. Szymánska et al. (2007) studied the interaction of drugs with Aβ immobilized onto Au-colloid modified electrode with cyclic voltammetry and electrochemical impedance spectroscopy. Islam et al. (2011) developed a microfludic biosensor for Aβ (1–42) detection using cyclic voltammetry. In this work, Aβ(1–42) induced the current change of colloidal gold nanoparticles (AuNPs)-covered electrode in $[Fe(CN)_6]^{3-}$ by the direct absorption of Aβ(1–42) onto the AuNPs surface. However, the selectivity inherent in the method was not examined since proteins can also absorb onto colloidal Au. Metal ions (e.g., Cu, Fe and Zn) found in Aβ plaques of the diseased brain can bind to Aβ and be linked to aggregation and neurotoxicity (Duce and Bush, 2010). Zhou's group investigated the interaction of Aβ and electrochemically active metal ions with cyclic voltammetry in solution (Jiang et al., 2010; Liu et al., 2011). Very recently, Pramanik et al. (2012) constructed an artificial platform for screening potential drugs that affect Aβ aggregation and toxic partially reduced oxygen species generation by the Aβ-Cu^{2+} and Aβ-heme complexes on the Aβ-modified electrode. However, to the best of our knowledge, there is no report on the sensitive and selective detection of Aβ peptides with electrochemical technique.

Because of the unique combination of chemical and physical properties, gold nanoparticles (AuNPs) coated with biological recognition elements have been widely used for the molecular recognition and signal amplification in diagnostics and detection (Omidfar et al., 2013). The rational design of the surface chemistry of AuNPs promotes specific interactions between receptors and analytes, rendering the measurements highly selective and sensitive. In the present work, we developed a simple, regenerable and sensitive voltammetric method for the detection of total Aβ peptides using AuNPs modified with Aβ(1–16)-heme complex (denoted as Aβ(1–16)-heme-AuNPs) on monoclonal antibody (mAb)-covered electrode. The method is based on the facts that: (1) the mAb is selective to the common N-terminus of all the Aβ species (Xia et al., 2010), (2) Aβ(1–16) is capable of binding to heme to form the Aβ(1–16)-heme complex (Atamna and Boyle, 2006; Atamna and Frey II, 2004; Azimi and Rauk, 2012; Pramanik et al., 2011; Pramanik et al., 2012; Yuan and Gao, 2013), and (3) heme complexes (e.g. Aβ(1–16)-heme, G-quadruplex-hemin) can catalyze the reduction of O_2 on electrode (Pramanik et al., 2012; Yang et al., 2012). As a result, Aβ(1–16)-heme-AuNPs captured by the mAb-covered electrode catalyzed the reduction of O_2 to H_2O_2. Pre-incubation of the electrode with Aβ peptides decreased the amount of Aβ(1–16)-heme-AuNPs immobilized onto the electrode, resulting in the decrease of the reduction current of O_2 to H_2O_2.

2. Experimental

2.1. Chemicals and reagents

1-Ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride (EDC), N-hydroxysulfosuccinimide (NHSS), ethanolamine (EA), 3-mercaptopropionic acid (MPA) and bovine serum albumin (BSA) were obtained from Sigma-Aldrich. Hemin was purchased from Aladdin reagent database Int. (Shanghai, China). Monoclonal antibody (clone 6E10) specific to the common N-terminus of Aβ peptide was obtained from Covance Inc. Peptides Aβ(1–16), Aβ(1–16)Cys (sequence: Asp-Ala-Glu-Phe-Arg-His-Asp-Ser-Gly-Tyr-Glu-Val-His-His-Gln-Lys-Cys), Aβ(1–40) and Aβ(1–42) were synthesized and purified by ChinaPeptides Co., Ltd (Shanghai, China). The supporting electrolyte was 10 mM phosphate-buffered saline solution (PBS buffer, pH 7.0) containing 50 mM Na_2SO_4. Other chemicals were analytical-grade reagents and were used without further purification. All aqueous solutions were prepared daily with deionzied water treated with a Millipore system (Simplicity Plus, Millipore Corp.).

The heme stock solution (1 mM) was prepared with 5 N NaOH. Samples of Aβ(1–40), Aβ(1–42) and antibody were diluted with 10 mM PBS buffer (pH 7.0). The Aβ stock solutions (0.1 mM) were prepared freshly as in our previous study (Jiang et al., 2010; Xia et al., 2010). Artificial cerebrospinal fluid (aCSF) comprising 150 mM NaCl, 3.0 mM KCl, 1.4 mM $CaCl_2$, 0.8 mM $MgCl_2$, 1.0 mM sodium phosphate and 3 μM BSA was prepared in-house.

2.2. Preparation and characterization of Aβ(1–16)-heme-AuNPs

The AuNPs of 13 nm were prepared using a trisodium citrate reduction method. The surface adsorption of Cys-containing peptides on AuNPs via Au–S bonds has been well documented in the literature (Araya et al., 2008; Kogan et al., 2006; Majzik et al., 2010; Xia et al., 2012). The Aβ(1–16)-AuNPs were prepared by ligand-exchange reaction between peptide Aβ(1–16)Cys and citrate-stabilized AuNPs. Briefly, the AuNPs was diluted with 1 mM PBS (pH 7.0) and mixed with Aβ(1–16)Cys at room temperature for 4 h. The immobilization ability of AuNPs for Aβ(1–16)Cys was studied by measuring the free Aβ(1–16)Cys in solution with mass spectroscopy, and the average number of Aβ(1–16)Cys molecules per gold nanoparticle was determined to be 315 ± 40. For the synthesis of Aβ(1–16)-heme-AuNPs, heme at the same concentration with Aβ (1–16)Cys was added to the Aβ(1–16)-AuNPs suspension. The synthesized Aβ(1–16)-heme-AuNPs were characterized by Cary 50 UV/vis spectrometry and FEI Tecnai G2 T20 transmission electron microscopy (TEM) (Fig. S1 in Supplementary material). We also found that the Aβ(1–16)-heme-AuNPs remain stable at pH 7.0 at least for one month. The Aβ(1–16)-heme-AuNPs were thoroughly rinsed with deionzied water to remove less amount of free Aβ(1–16) and heme, and diluted with 1 mM PBS solution prior to use.

2.3. Detection of Aβ

The MPA self-assembled monolayers (SAMs) were formed by immersing the cleaned gold electrode in an ethanol solution of 10 mM MPA in the darkness for 12 h. This step was followed by washing the electrode thoroughly with ethanol and water. The mAb-covered electrode was performed by cross-linking mAb molecules onto the SAM via the EDC/NHSS-mediated amine coupling reaction (Haes et al., 2005; Liu et al., 2013). Briefly, the MPA-covered electrode was soaked in a solution comprising of 0.2 M EDC and 0.1 M NHSS for 15 min, washed with water and soaked in a 1 μM mAb solution for 12 h. This was followed by casting 0.2 mM ethanolamine onto the electrode to block the unreacted sites for 5 min. The capture of Aβ or Aβ(1–16)-heme-AuNPs was performed at room temperature by casting a given concentration of Aβ solution or Aβ(1–16)-heme-AuNPs suspension onto the mAb-covered electrode for 10 min. After the electrode had been rinsed with water to remove the excess physiadsorbed Aβ(1–16)-heme-AuNPs, voltammetric determination in the air-saturated supporting electrolyte was performed on a DY2013 electrochemical work station (Digi-Ivy, Inc., Austin, TX) using a home-made plastic electrochemical cell. A platinum wire and a Ag/AgCl electrode were used as the auxiliary and the reference electrodes, respectively. After each assay, the electrode surface was regenerated with 10 mM NaOH for 5 min (desorbing the target Aβ and Aβ(1–16)-heme-AuNPs).

3. Results and discussion

3.1. Principle of the electrochemical assay for Aβ

Recent studies show that heme can bind to Aβ peptide to form the Aβ-heme complex behaving as a peroxidase enzyme (Atamna and Boyle, 2006; Pramanik et al., 2011; Pramanik et al., 2012). The major binding site is believed to be one of the three His residues in the N-terminus, especially at the position His^{13} (Pramanik et al., 2012; Yuan and Gao, 2013). Pramanik et al. (2012) suggested that the Aβ(1–16)-heme complexes immobilized onto gold electrode showed strong electrocatalytic reduction of O_2 to H_2O_2. The schematic representation of our voltammetric assay for the detection of Aβ with Aβ(1–16)-heme-AuNPs is illustrated in Fig. 1. The mAb specific to the amino acids 3–8 of Aβ was immobilized onto the MPA SAMs through the standard amine coupling reaction. The strong and specific antibody–Aβ interaction (Ramakrishnan et al., 2009; Xia et al., 2010) allows Aβ(1–16)-heme-AuNPs to be anchored onto the electrode surface (*cf.* the top of Fig. 1). The electrochemical signals from the reduction of O_2 to H_2O_2 catalyzed by Aβ(1–16)-heme-AuNPs would be observed. Since Aβ(1–16)-functionalized AuNPs may absorb other components in the real sample analysis, the competitive assay for Aβ detection was performed by incubating the electrode successively with Aβ solution and Aβ(1–16)-heme-AuNPs. If the Aβ-binding site in the mAb was occupied by the native Aβ, Aβ(1–16)-heme-AuNPs would be incapable of anchoring onto the electrode (*cf.* the bottom of Fig. 1). Consequently, poor electrochemical signal from the reduction of O_2 was observed. We anticipate that total Aβ species could be detected with this method since the mAb is capable of binding to the N-terminus of all the Aβ species. Note that one mAb molecule can bind one Aβ molecule or one Aβ(1–16)-heme-modified gold nanoparticle, and each gold nanoparticle can absorb large numbers of Aβ(1–16)-heme; thus, the electrochemical signals will be greatly amplified.

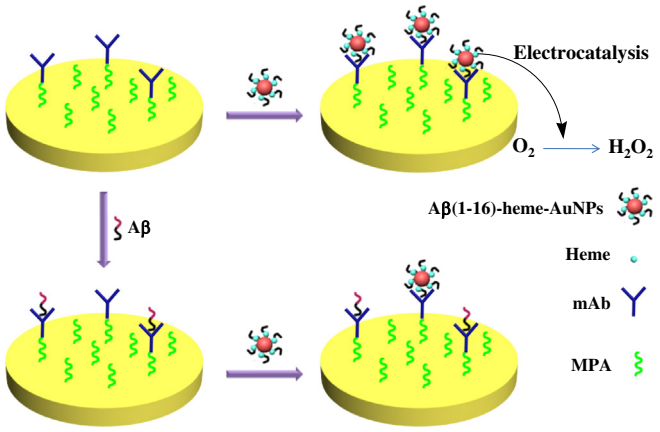

Fig. 1. Schematic representation of Aβ detection. More Aβ(1–16)-heme-AuNPs are attached onto the mAb-covered electrode without the Aβ capture step (top). A smaller number of Aβ(1–16)-heme-AuNPs are attached after incubation of the electrode with Aβ species (bottom).

3.2. Feasibility for Aβ detection

Fig. 2A shows the voltammetric response acquired at the mAb-covered electrodes after attachment of different concentrations of Aβ(1–16)-heme-AuNPs. The electrochemical response reveals a reduction peak at around −455 mV, which is attributed to Aβ(1–16)-heme-promoted O_2 reduction (Pramanik et al., 2012). The currents increase with the increase of the number of captured Aβ(1–16)-heme-AuNPs. The dependence of the reduction current on the Aβ(1–16)-heme-AuNPs concentration is presented in the Supplementary material (Fig. S2). Beyond 1.20 nM, the currents at −455 mV begin to level off. Interestingly, we found that the current–concentration relationship can be fitted with the Langmuir isotherm. The binding affinity (K_A) between mAb and Aβ(1–16)-heme-AuNPs from the fits was deduced to be 3.38 nM^{-1}. The nanomolar level K_A value suggests that the binding of the mAb to Aβ(1–16)-heme-AuNPs is rather high. This value is in agreement with the reported nanomolar level K_D value between mAb and Aβ, indicating that the attachment of Aβ(1–16)-heme-AuNPs on the mAb-covered electrode results from the specific antibody–Aβ interaction.

Current clinical practice of AD diagnostics is based on the detection of Aβ(1–42) or total Aβ species (Golde et al., 2000). To demonstrate the amenability of our method to the analysis of total Aβ, we tested Aβ(1–40) and Aβ(1–42). Black curve in Fig. 2B is a representative cyclic voltammogram (CV) collected at the mAb-covered electrode after the capture of Aβ(1–16)-heme-AuNPs. Incubation of the electrode with the Aβ(1–40) or Aβ(1–42) solution before the capture of Aβ(1–16)-heme-AuNPs resulted in a much attenuated peak current (*cf.* the red and blue curves), indicating that the Aβ-binding site in mAb was occupied by Aβ(1–40) or Aβ(1–42). Moreover, these results also demonstrate that incubation of the electrode with Aβ(1–16)-heme-AuNPs suspension did not lead to the loss of captured Aβ. This is understandable since the bulk mass of Aβ(1–16)-heme-AuNPs is probably unfavorable for the exchange between Aβ(1–16)-heme-AuNPs and anchored Aβ. In addition, a real CSF sample contains approximately 150–400 mg/L plasma proteins (Liu et al., 2012). The control experiment (green curve) was conducted with serum albumin instead of Aβ.

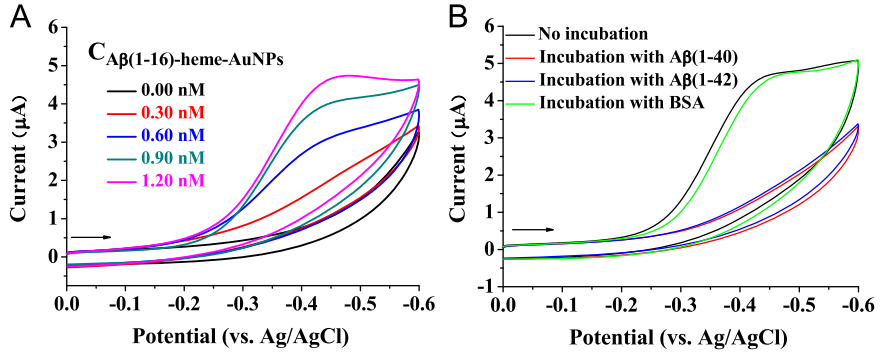

Fig. 2. (A) Cyclic voltammograms (CVs) acquired at mAb-covered electrodes after the attachment of different concentrations of Aβ(1–16)-heme-AuNPs. (B) CVs showing the competitive assay for Aβ species. In panel B, the concentrations of Aβ(1–16)-heme-AuNPs, Aβ(1–40), Aβ(1–42) and BSA were 1.80, 2.00, 2.00 nM and 3.00 μM, respectively. The scan rate was 50 mV/s, and the arrow indicates the scan direction. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

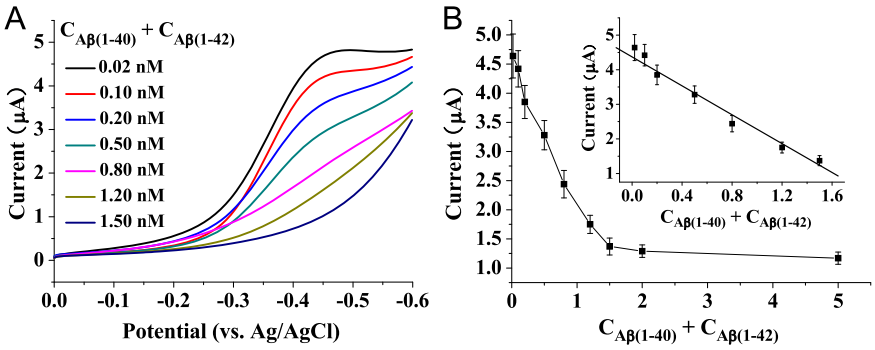

Fig. 3. (A) Representative CVs collected at mAb-covered electrode with exposing to different concentrations of Aβ solutions before the attachment of Aβ(1–16)-heme-AuNPs. (B) Plots of the reduction current at −455 mV against the Aβ concentrations (0.02–5.00 nM). The inset in panel B shows the linear plots at concentrations of 0.02, 0.10, 0.20, 0.50, 0.80, 1.20 and 1.50 nM. Each point was averaged from at least three replicates, and RSDs are shown as the error bars. The other experimental conditions are the same as those in Fig. 2.

As a result, there is no apparent difference in the reduction wave (*cf.* black and green curves), indicating that the sensor is selective to Aβ species. The good selectivity is attributed to the strong antibody–antigen interaction between mAb and Aβ.

Previously, Xia et al. suggested that Aβ bound to antibody can be desorbed by NaOH solution. We also found that the electrode can be conveniently regenerated by immersing the electrode in 10 mM NaOH solution and then rinsing the surface with water (i.e., desorbing Aβ peptides and Aβ(1–16)-heme-AuNPs bound to the mAb). No apparent change in the reduction current was observed after eight regeneration/assay cycles. Thus, multiple samples can be determined using one electrode, dramatically increasing the sample throughput and reducing the analysis time and cost. In addition, we found that the relative standard deviations (RSDs) are all below 18% at three different electrodes in parallel.

3.3. Sensitivity and artificial samples detection

With the regeneration of the method established, we further evaluated other analytical merits (e.g. reproducibility, sensitivity and dynamic range). The Aβ samples were prepared by mixing Aβ (1–40) and Aβ(1–42) in the Aβ(1–40)/Aβ(1–42) ratio of 6:1, which is close to the real ratio in human CSF (Xia et al., 2010). As shown in Fig. 3A, the reduction currents decrease with the increase of Aβ concentrations. The dependence of the reduction currents on the concentrations of total Aβ is presented in Fig. 3B. The aforementioned regeneration of the electrode surface contributes to acceptable reproducibility of the method, as the RSDs, shown as the error bars in Fig. 3B, are all less than 11%. The inset in Fig. 3B is the linear portion of the calibration curve between 0.02 and 1.50 nM, which is expressed as current (μA)=4.37−2.09 $C_{Aβ}$ (nM) (R^2= 0.988). The detection limit (3 s) of the method was estimated to be 10 pM (n=11). This value is comparable to that obtained by SPR with the signal amplification of streptavidin-antibody conjugate (Xia et al., 2010), and is at least four orders lower than that achievable by capillary electrophoresis (Picou et al., 2010). The high sensitivity is attributed to the signal amplification of AuNPs and the enzyme-like catalytic activity of Aβ(1–16)-heme to O_2 reduction. In human CSF, the basal level of Aβ is at nanomolar scale (Southwick et al., 1996). Thus, the strategy developed in this study is promising to detect Aβ in body fluids.

To demonstrate the viability of the method for the analysis of total Aβ species in real sample, we carried out the measurement of amounts of Aβ in aCSF (*cf.* Fig. S3 in Supplementary material). No Aβ was found in aCSF; thus, 0.30 nM of Aβ(1–40) and 0.30 nM of Aβ (1–42) were added into the aCSF and then analyzed. The reduction current at −455 mV was determined to be 3.24 μA and the content of Aβ was deduced to be 0.54 nM by the calibration curve. To ascertain the exactitude of the method for the assay of total Aβ, we further tested the sample spiked with 0.20 nM of Aβ(1–16) and the concentration was determined to be 0.77 nM, which is close to the known content of 0.80 nM. These results confirmed that the present method could offer a useful means for quantifying Aβ in a biological matrix.

4. Conclusion

We, for the first time, reported an electrochemical strategy for the sensitive detection of total Aβ using Aβ(1–16)-heme-AuNPs. Aβ(1–16)-heme-AuNPs captured by the mAb-covered electrode facilitated the reduction of O_2. Pre-incubation of the electrode with native Aβ prevented Aβ(1–16)-heme-AuNPs from binding to the immobilized mAb on electrode. By the competitive assay, low level of Aβ can be readily detected with excellent regeneration and reproducibility. The detection limit was estimated to be 10 pM, which is comparable to that obtained by SPR with the signal amplification of streptavidin-antibody conjugate and is at least four orders lower than that achievable by capillary electrophoresis. In addition, the method remains much faster and simpler than the existing methods without the requirement of expensive and complicated instruments. We believe that our work would be valuable in the design of new types of electrochemical biosensors for the detection of peptides and proteins.

Acknowledgments

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.bios.2013.05.028.

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