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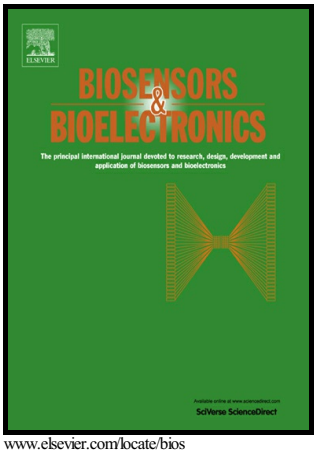

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Carbohydrate-based electrochemical biosensor for detection of a cancer biomarker in human plasma

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ABSTRACT

Autocrine motility factor (AMF) is a tumor-secreted cytokine that stimulates tumor cell motility in vitro and metastasis in vivo. AMF could be detected in serum or urine of cancer patients with worse prognosis. Reported as a cancer biomarker, AMF secretion into body fluids might be closely related to metastases formation. In this study, a sensitive and specific carbohydrate-based electrochemical biosensor was designed for the detection and quantification of a protein model of AMF, namely phosphoglucose isomerase from rabbit muscle (RmPGI). Indeed, RmPGI displays high homology with AMF and has been shown to have AMF activity. The biosensor was constructed by covalent binding of the enzyme substrate D-fructose 6-phosphate (F6P). Immobilization was achieved on a gold surface electrode following a bottom-up approach through an aminated surface obtained by electrochemical patterning of ethylene diamine and terminal amine polyethylene glycol chain to prevent non-specific interactions. Carbohydrate-protein interactions were quantified in a range of 10 fM to 100 nM. Complex formation was analyzed through monitoring of the redox couple Fe^{2+}/Fe^{3+} by electrochemical impedance spectroscopy and square wave voltammetry. The F6P-biosensor demonstrates a detection limit of 6.6 fM and high selectivity when compared to other non-specific glycolytic proteins such as D-glucose-6-phosphate dehydrogenase. Detection of protein in spiked plasma was demonstrated and accuracy of 95% is obtained compared to result obtained in PBS (phosphate buffered saline). F6P-biosensor is a very promising proof of concept required for the design of a carbohydrate-based electrochemical biosensor using the enzyme substrate as bioreceptor. Such biosensor could be generalized to detect other protein biomarkers of interest.

1. Introduction

Cancer is a major cause of mortality in economically developed and developing countries. Thus development of efficient diagnostic tools is the subject of intensive research. The discovery of efficient tumor markers and the approach of their detection is important in the case of diagnosis and therapy approaches. Various cancer biomarkers are now well known and demonstrate high efficacy in prognostic of some cancers, including proteins, antigens, hormones, receptors, genetic markers, and microRNAs (Füzéry et al., 2013). Most biomarkers currently in use are cell surface or secreted proteins (Brooks, 2012), such as prostate specific antigen (PSA), interleukin 6 (IL-6), interleukin 8 (IL-8), carcino-embryonic antigen (CEA), cancer antigens (CA-125, CA15-3, CA19-9, CA27-29), c-reactive protein (CRP), p53 protein, thyroglobuline, and α-fetoprotein (AFP) (Chikkaveeraiah et al., 2012).

Autocrine motility factor (AMF) is an extracellular protein which has the properties of stimulating the active migration of tumor cells in an autocrine manner (Liotta et al., 1986; Watanabe et al., 1996). AMF has been described to have anti-apoptotic activity (Haga et al., 2003; Yanagawa et al., 2004), and to act in a paracrine manner for endothelial cells as an angiogenic factor (Funasaka et al., 2001). Interaction of AMF with the tumor cell receptor AMFR/gp78 is known as a crucial parameter in tumor cells motility in vitro and metastases development in vivo (Watanabe et al.,