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Review

Proteomic detection of nitroproteins as potential biomarkers for cardiovascular disease

*Mutay Aslan**, *Serdar Dogan*

Akdeniz University Faculty of Medicine, Department of Medical Biochemistry, Campus, 07070 Antalya, Turkey

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ABSTRACT

Increased levels of reactive oxygen and nitrogen species are linked to many human diseases and can be formed as an indirect result of the disease process. The accumulation of specific nitroproteins which correlate with pathological processes suggests that nitration of protein tyrosine represents a dynamic and selective process, rather than a random event. Indeed, in numerous clinical disorders associated with an upregulation in oxidative stress, tyrosine nitration has been limited to certain cell types and to selective sites of injury. Additionally, proteomic studies show that only certain proteins are nitrated in selective tissue extracts. A growing list of nitrated proteins link the negative effects of protein nitration with their accumulation in a wide variety of diseases related to oxidation. Nitration of tyrosine has been demonstrated in diverse proteins such as cytochrome c, actin, histone, superoxide dismutase, α-synuclein, albumin, and angiotensin II. In vitro and in vivo aspects of redox-proteomics of specific nitroproteins that could be relevant to biomarker analysis and understanding of cardiovascular disease mechanism will be discussed within this review.

Contents

* *Corresponding author at:* Akdeniz University Medical School, Department of Biochemistry, 07070 Antalya, Turkey. Tel.: +90 242 2496393; fax: +90 242 2496891.
E-mail address: mutayaslan@akdeniz.edu.tr (M. Aslan).

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1. Introduction

Cardiovascular diseases (CVD) are a group of disorders of the heart and blood vessels that include: coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis and pulmonary embolism. The leading cause of death from CVD is estimated to be 17.1 million people each year, representing 29% of all global deaths [1]. Of these deaths, an estimated 7.2 million are due to coronary artery disease (CAD). The mortality due to CVD is reported to be 82% in low- and middle-income countries which is greater when compared to more developed regions. It is estimated that by 2030, almost 23.6 million people will die from CVD, mainly from heart disease [1].

Numerous medical research is done to understand the pathophysiology of CVD, to establish new diagnostic biological markers (biomarkers) and develop new therapeutic procedures. Cardiovascular disease is the arena in which biomarkers have been extensively evaluated [2]. Biomarkers in CVD are used to point out the formation of atherosclerosis [3], diagnose acute myocardial infarction (AMI), risk-stratify patients with acute coronary syndromes (ACS), aid in the diagnosis of chronic as well as acute heart failure, provide prognostic information to help in the targeting of therapies associated with increased cardiovascular risk and to rule-out deep-vein thrombosis and pulmonary embolism [2].

2. Biomarker, definition, characteristics and sources

A biomarker is defined as an objectively measured and evaluated indicator of normal biological processes, pathogenic processes or pharmacological response to a therapeutic intervention [4]. If a biomarker or panel of markers is to be used to justify regulatory decision making, the assay used to measure that marker (*biomarker assay*) must demonstrate specificity, accuracy, robustness, validity and clinical utility [5]. According to the FDA's pharmacogenomic guidance document [6], a valid biomarker is "a biomarker that is measured in an analytical test system with well-established performance characteristics and for which there is an established scientific framework or body of evidence that elucidates the physiologic, toxicologic, pharmacologic, or clinical significance of test results".

Biomarkers are used in the determination of disease stage, as diagnostic tools, as indicators of disease prognosis and as predictors of clinical response to a certain intervention [4]. If the concentration of a biomarker in a patient sample correlates with the presence of a certain disease, then determining the change in the measured levels of the biomarker will facilitate screening of individuals at high risk and thus allow the detection of the disease at an early stage. Early recognition of an ongoing pathology is an important factor that will have impact on the probability of successful treatment [7].

According to the Food and Drug Administration (FDA), characteristics of an ideal biomarker are sensitivity, specificity, accuracy, predictability, robustness, reproducibility, simplicity for routine use without the need for sophisticated equipment or operator skill. An ideal biomarker should also have sensitivity and specificity to pharmacological treatment without interference from other therapy [8]. Thus it is required to have specificity and sensitivity towards a given disease. In theory, every disease maybe uncovered and characterized by a unique biomarker. A biomarker should be considered as a panel of up- and down-regulated protein modifications that differ in disease and normal state. Biomarkers may also have altered posttranslational modifications [9].

The accessibility to the source of a biomarker is important in biomarker research. Whole blood, serum, plasma, urine, amniotic fluid, cerebrospinal fluid, synovial fluid, and nipple aspirate fluid are the main sources for biomarkers. Blood as a source for biomarkers is easily accessible and its collection is minimally invasive, low risk and cheap. Tissue-related proteins can be released into the blood stream via secretion, shedding from surface and non-specific leakage [10].