REVIEW ARTICLE

Folia Cardiologica 2019
tom 14, nr 1, strony 60–66

ISSN 2353–7752

New biomarkers in cardiology — are we on the right track?

Nowe markery biologiczne w kardiologii — czy właściwy trop?

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Artykuł jest tłumaczeniem pracy: Tymińska A, Filipiak KJ. Nowe markery biologiczne w kardiologii — czy właściwy trop? Folia Cardiol. 2019; 14 (1): 52–59. DOI: 10.5603/FC.a2018.0060. Należy cytować wersję pierwotną

Abstract

There are many markers for the risk assessment of cardiovascular diseases. New sensitive and specific biomarkers that could help stratify risk, in both healthy and cardiovascular populations, are still being sought. Galectin 3 and ST-2 seem to be very promising molecules. However, further research is needed to establish their full diagnostic and prognostic value. We present a review of the literature showing the possibility of comprehensive use of both biomarkers, especially in coronary artery disease. Galectin-3 and ST-2, through their association with fibrotic processes, may prove to be beneficial in patients with coronary disease and following myocardial infarction.

Key words: cardiovascular diseases, coronary artery disease, galectin-3, myocardial infarction, remodelling, ST-2

Folia Cardiologica 2019; 14, 1: 60–66

Introduction

Cardiovascular diseases (CVD) belong to the group of chronic diseases usually developing throughout life. CVDs are the most common cause of death in Poland (46%) and at the same time they are characterized by increasing morbidity [1]. Therefore, it is important to have indicators to improve the diagnostic process of CVD at different stages of the disease, and prognosis of risk level. The most common CVD is coronary artery disease. Proven indicators in the assessment of the initial stages of atherosclerosis include: IMT, intima–media thickness, PMV, pulse wave velocity, ABI, ankle-brachial index, assessing all types of serum cholesterol fractions. However, the evaluation of troponin dynamics is a key element in the diagnosis of myocardial necrosis [2, 3]. Recently there has been an increased interest in new biochemical markers. Consistent evidence from prospective studies is needed if we wanted to add them to the new diagnostic algorithms.

The following paper summarises current knowledge on the characteristics and potential use of galactin 3 (Gal-3) and ST-2 protein (suppression of tumorigenicity 2) in cardiology, especially in coronary artery disease.

Biological characteristics of Gal-3 and ST-2 proteins

Gal-3 is a representative of galectins belonging to the family of carbohydrate-binding proteins (lectins) [4, 5]. It has a domain structure consisting of: a short N-terminal domain, collagen-like and atypical C-terminal domain within which there is a carbohydrate recognizing domain (CRD), thanks to which Gal-3 interacts with a significant number of ligands, *e.g.* receptors located on the cell surface, as

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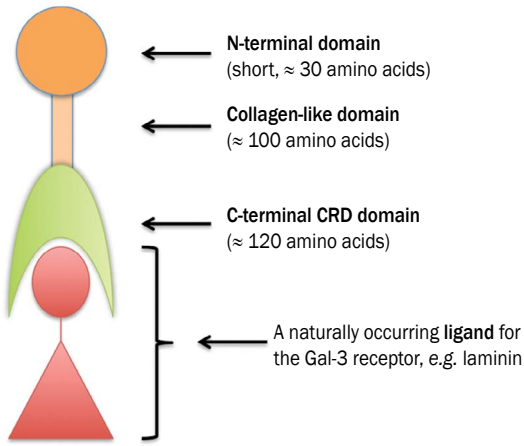


Figure 1. Structure of galectin 3 (Gal-3) (based on [6]); CRD — carbohydrate recognition domain

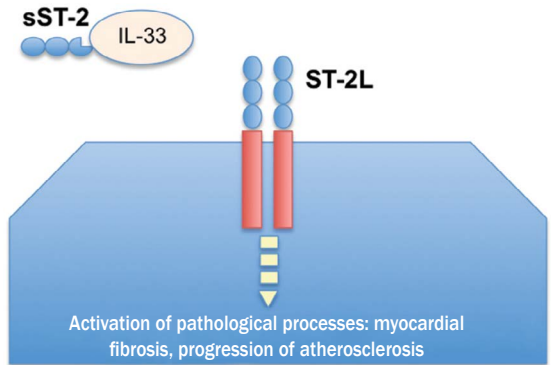


Figure 2. Structure of transmembrane and soluble form of ST-2 (sST-2) protein and the mechanism of their action. Increased sST-2 concentration prevents the binding of interleukin 33 (IL-33) to the ST-2 ligand (ST-2L) protein, contributing to adverse changes in the heart structure

well as with extracellular space proteins, modulating intercellular adhesion [4, 6] (Figure 1). It is found mainly in the cytoplasm, while its expression occurs in many types of cells, including macrophages, neutrophils, fibroblasts, cancer cells, and is involved in inflammatory responses and the fibrosing processes [4, 5].

The ST-2 protein belongs to the superfamily of Toll receptors binding interleukin 1 (TIR, Toll/interleukin-1 receptor) [7]. It has two clinically significant forms - transmembrane and soluble. The transmembrane form (ST-2L, ST-2 ligand) is present mainly on inflammatory cells, cardiomyocytes and endothelium. Animal studies have shown that interleukin 33 (IL-33) interacts with ST-2L present on cardiomyocytes to prevent myocardial hypertrophy and fibrosis [7]. The soluble form (sST-2, soluble ST-2) circulates freely in the blood and it is possible to measure its concentration in a standard biochemical blood test [7, 8]. The release of sST-2 is regulated by fibroblasts which are stimulated for growth and by pro-inflammatory cytokines, *e.g.* tumour necrosis factor α (TNF-α) and interleukin 6 (IL-6) [8]. Excessive concentration of sST-2 prevents the binding of IL-33 to the ST-2L protein, contributing to the occurrence of adverse changes in the heart structure [8]. It is said that IL-33/ST-2 interaction, apart from participation in fibrosis and myocardial remodeling also takes part in atherosclerosis progression [8] (Figure 2).

New perspectives for the use of biomarkers in clinical practice

Coronary artery disease

The role of inflammatory process in the pathogenesis of atherosclerosis is emphasized. Currently, sensitive inflammatory biomarkers are being searched for, which could help in early and effective identification of patients with increased risk of coronary artery disease, as well as to predict responses to treatment and assess prognosis.

Myocardial infarction (MI) leads to myocardial necrosis and structural and biochemical changes in damaged tissues. These changes include deposition of collagen with scarring, fibrosis, hypertrophy and a change in the volume of the heart cavities, which is referred to as remodeling and leads to the development of heart failure. It is worth emphasizing that post-infarct remodeling also involves tissues which did not undergo ischemia with the aim of maintaining systolic and diastolic heart function [9].

According to the nationwide AMI-PL database (Nationwide Acute Myocardial Infarction Database in Poland), nearly 80% of patients with ST-elevation myocardial infarction (STEMI) are subjected to coronary revascularization [10]. Improved treatment of acute coronary syndromes with percutaneous coronary intervention (PCI) reduces in-hospital mortality however, also leaves a large group of patients with left ventricular injury [3]. According AMI-PL database, in patients after MI, heart failure was one of the most frequent cause of repeated hospitalizations [10].

The role of Gal-3 in coronary artery disease

Gal-3 concentration is significantly higher in patients with coronary artery disease, in which an inflammatory substrate is one of the main causes of macrophage activation [11]. In addition, Gal-3 can affect the development of atherosclerotic plaques by preventing the effective removal of low-density lipoproteins (LDL) [12]. It is known that Gal-3 expression is clearly marked in unstable atherosclerotic plaques [11]. The role of Gal-3 in the development of atherosclerosis is supported by the results of both in vivo and in vitro studies. MacKinnon et al. demonstrated that

pharmacological blocking of Gal-3 in a mouse significantly inhibited the development of atherosclerotic plaque [13].

In experimental studies, a higher expression of Gal-3 mRNA was observed in the early post-infarction period, with the maximum reached during the first week, and a gradual decrease in the following weeks. The concentration of Gal-3 also increased in the surrounding tissues which were not directly affected by ischemia, in which the maximum expression was already reached on day 1 [14]. An increase in Gal-3 concentration in the early post-infarction period seems to contribute to the activation of repair functions in the damaged zone in order to preserve the geometry and function of the heart [15]. However, in the longer term, chronic activation leads to tissue fibrosis and accelerated unfavourable remodeling of the heart [15].

In a study conducted by Tsai et al. of a 196 group of patients with acute STEMI showed that Gal-3 concentration increases in the first hours after PCI and is an independent prognostic factor of death and development of heart failure in the early (30-day) post-infarction period, regardless of the severity of coronary artery lesions, left ventricular ejection fraction (LVEF) and serum creatinine concentration [16]. However, it should be noted that Gal-3 is an important biomarker of fibrosis, and its expression also increases in the course of cirrhosis or progressive kidney fibrosis. Deterioration of renal function in the course of heart failure may have a significant effect on Gal-3 concentration, which may affect its prognostic value [17].

In the study carried out by Szadkowska et al. [18], patients after MI with elevated Gal-3 concentration during hospitalization were characterized by a higher risk of developing heart failure and atrial fibrillation (AF) *de novo*. However, the authors did not observe correlation between the concentration of Gal-3 and LVEF after MI, whereas such correlation was documented for N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity C-reactive protein (hsCRP) [18].

In a study conducted by Weir and his team in a group of 100 patients after STEMI, each patient had a Gal-3 concentration measurement and magnetic resonance imaging (MRI) of the heart at the beginning of the study and after 4 months. There was no correlation between Gal-3 concentration, LVEF and left ventricular volumes assessed in MRI initially, but the reverse correlation between Gal-3 and LVEF was observed after 4 months of observation. Moreover, throughout the study a correlation between Gal-3 and NT-proBNP concentrations and extracellular matrix proteins such as matrix metalloproteinase 3 (MMP-3), tissue inhibitor of matrix metalloproteinases 1 (TIMP-1), monocyte chemoattractant protein 1 (MCP-1) and interleukin-8 (IL-8) was observed [19]. In the same group, a correlation between a higher Gal-3 concentration and more intensive remodeling was observed in patients with preserved LVEF (referred to as LVEF > 49. 2%), in the early post-infarction period, but not in patients with severe left ventricular dysfunction [19]. In a study carried out by van der Velde et al. [20], the concentration of Gal-3, evaluated immediately after MI, predicted the LVEF value and the size of post-infarction scar after 4 months [20].

To sum up, there is a link between Gal-3 concentration and the increased risk of developing heart failure after MI. However, due to the small groups participating in the studies and the short observation time, the conclusions of the studies so far are still limited.

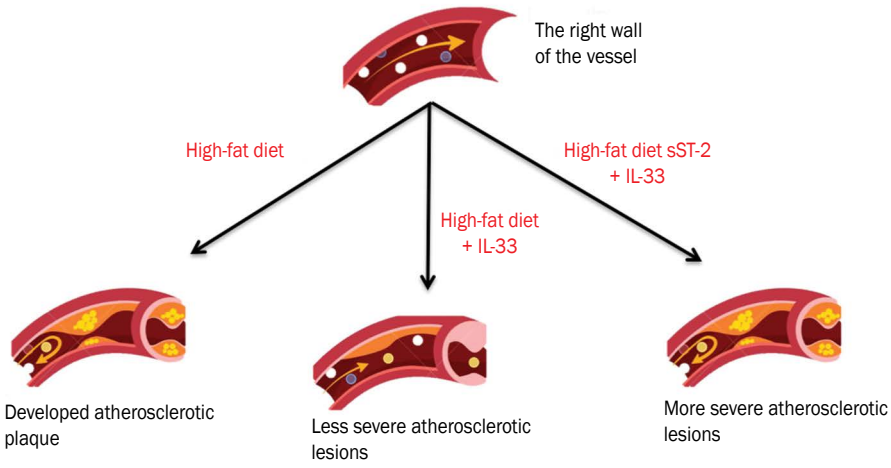
The role of ST-2 protein in coronary artery disease

The role of ST-2 protein was also studied in ischemic heart disease. It is believed that by assessing the ST-2 protein it is possible to predict cardiovascular prognosis, including the risk of death in patients with coronary artery disease, although its diagnostic use is limited.

Seki et al. have shown that IL-33 binding to the transmembrane form of ST-2 causes activation of the nuclear factor (NF)-κB, thanks to which it can regulate the survival of cells [21]. In a rat study, subcutaneous injection of IL-33 resulted in inhibition of apoptosis induced by ischemia through increased expression of proteins responsible for apoptosis inhibition and decreased activation of caspase 3, an enzyme which increases the process of apoptosis. This led to a decrease in the volume of MI and fibrosis [21].

In addition, it is considered that IL-33/ST-2 protein pathway is associated with the pathogenesis of atherosclerosis. It is believed that active inflammation is the cause of instability of some atherosclerotic lesions, leading to rupture of the plaque and subsequent formation of clots, leading to vessel closure and MI. One of the strategies of inhibiting the inflammatory process in vessels in the course of atherosclerosis may be an increased share of Th2 immune cells. The IL-33/ST2 system can be one of the ways leading to their activation. Mice without apolipoprotein E gene, fed a high-fat diet have high serum cholesterol levels and develop atherosclerosis. Mice treated with IL-33 showed a reduced number of atherosclerotic plaques and lower levels of serum antibodies to oxidized LDL compared to control mice. On the other hand, after the initial supply of soluble ST-2 form, even before exposure to IL-33, these mice showed increased arteriosclerosis in comparison to those untreated with sST2 (effect of anti-IL-33 soluble isoform ST2) (Figure 3) [7].

By reducing the concentration of interferon γ, IL-33 stimulates macrophages to produce metalloproteinases (MMPs), prevents the destruction of the extracellular matrix and atherosclerotic plaque destabilization [22]. The concentration of MMPs is particularly high in the acute phase of MI [22]. Guzel et al. [23] found that serum IL-33 concentration is significantly lower in patients with



Figures 3. Interleukin 33 (IL-33)/ST2 system reduces the progression of atherosclerosis (based on [7]); sST-2 — soluble ST-2

non-ST-elevation myocardial infarction (NSTEMI) than in the control group and correlates negatively with MMP-9 level. An increase in sST-2 and a parallel decrease in IL-33 concentration [23] during MI may indicate an increased degree of myocardial injury.

Many studies have shown that the soluble form of ST-2 is an important biomarker after MI [21, 24, 25]. The sST-2 concentration increases several hours after MI. It has been observed that the counteraction to the protective properties of IL-33 depends on the concentration of sST-2 [21]. Moreover, Richards et al. [24] team observed that early assessment of sST-2 concentration has the best prognostic value. Shimpo et al. [25] proved assessment sST-2 in patients after acute STEMI has a predictive value. Patients with higher sST-2 serum levels had a significantly higher risk of death or occurrence of newly diagnosed heart failure within 30 days [25], although this relationship lost relevance when B-type natriuretic peptide (BNP) and cardiac troponin I (cTnI) () were included in multivariate analysis [25]. Jenkins et al. [26] in a study of 1400 patients after MI assessed the predictive value in long-term, 5-year observation. Elevated sST-2 concentrations were found in half of patients with MI, and higher concentrations were associated with a high risk of death and development of heart failure regardless of other predictors, such as age, gender, co-morbidities, troponin T, or Killip class [26]. This indicates the need for further research to assess the usefulness of ST-2 in predicting the risk of developing heart failure after MI.

Interestingly, the CLARITY-TIMI 28 study (CLopidogrel as Adjunctive Reperfusion TherapY-Thrombolysis in Myocardial Infarction 28) of patients after STEMI proved that ST-2 protein is an independent prognostic factor and adding it to TIMI Risk Score improves prognostic evaluation of patients after STEMI. Sabatine and colleagues showed that the combination of ST-2 protein with NT-proBNP significantly improves risk stratification in coronary artery disease [27]. On the contrary, no improvement in risk stratification was demonstrated after including of ST-2 protein to the GRACE scale in patients after NSTEMI [28].

Weir et al. [29] observed that in patients after acute MI sST-2 concentrations were positively correlated with the extent of MI and predicted unfavourable left ventricular remodeling evaluated by MRI during 24-week observation. The change in sST-2 concentration (evaluated initially and after 24 weeks) was associated with a significant change in left ventricular end-diastolic volume [29]. sST-2 has not been shown to predict for the recurrence of MI [24].

The role of biomarkers in other clinical situations

It has been demonstrated that higher Gal-3 concentrations are associated with a higher risk of AF development in a 10-year observation period, regardless of age and gender [30]. However, this relationship was not observed after taking into account other typical risk factors of AF development [30]. Elevated Gal-3 levels were also observed in patients with persistent AF without coexisting structural heart disease [31]. However, it is still unclear whether the Gal-3 assessment may be helpful in identifying those patients with AF in whom pulmonary venous isolation surgery would bring the greatest benefits [31, 32]. Controversial data also concern the assessment of the risk of recurrence of arrhythmia after ablation [31, 32]. Chen and his team studied the sST-2 concentrations in patients with AF not associated with mitral stenosis or valvular prosthesis and in patients with sinus rhythm. They

observed higher sST-2 concentrations in patients with AF, and a positive correlation with left atrial size. There were no differences between patients with paroxysmal and persistent AF. During a 6-month observation period, they demonstrated that sST-2 and left atrial size are independent factors of heart failure development in patients with so-called non-valvular AF [33].

On the basis of numerous studies the importance of ST-2 and Gal-3 proteins in chronic and acute heart failure have been proven. This was reflected in the guidelines of the American Heart Association (AHA), in which ST-2 and Gal-3 proteins were recognized as valuable additional diagnostic and prognostic markers in acute and chronic heart failure (recommendation class IIb, proof level B) [34]. The predictive power of both biomarkers has been shown to increase in combination with NT-proBNP. Furthermore, heart failure therapy strategies based on measurements of several biomarkers can bring additional benefits.

In a multicentre Framingham Heart Study, sST-2 concentration increased with age and was associated with higher blood pressure, more frequent use of hypotensive drugs and more frequent coexistence of diabetes [35]. Higher ST-2 protein concentrations were also observed in patients with aortic stenosis [36]. The natural course of this heart defect leads to overload of the left ventricle and its hypertrophy, and then to fibrosis and remodeling of the heart muscle. Sundl and his team evaluated the relationship between sST-2 concentrations measured before transcatheter aortic valve implantation (TAVI) and the prognosis [37]. The baseline sST-2 > 29 ng/ml concentration has been shown to be associated with unfavourable prognosis after TAVI procedure and may be useful in predicting short and long-term mortality. However, the sST-2 protein did not show any advantage over NT-proBNP or currently used surgical risk assessment algorithms (EuroSORE II, STS_PROM) [37].

Wojciechowska et al. [38] demonstrated that ST-2 protein may be useful in the assessment of prognosis in patients with dilated cardiomyopathy. Moreover, in hypertrophic myocardial model or during active myocardial inflammation there is a significant infiltration of activated macrophages with increased Gal-3 concentrations [39]. The MADIT-CRT (Multicenter Automatic Implantation Trial With Resynchronization Therapy) subanalysis evaluated the benefit of cardiac resynchronization therapy in patients with symptoms of low severity heart failure (I–II class of New York Heart Association [NYHA]) depending on Gal-3 concentration. It was shown that patients with higher Gal-3 concentrations benefited more from this therapy [40]. The authors suggest that elevated Gal-3 concentration in this subgroup of patients with heart failure indicates the ongoing processes of fibrosis, which means that these patients may respond better to cardiac resynchronization therapy (CRT) therapy and its anti-fibrosis properties as well as the process of myocardial remodeling [40].

New therapeutic perspectives

Assuming that Gal-3 and ST-2 protein are associated with the risk of developing post-infarction heart failure, it may be hypothesized that the use of treatments to reduce unwanted remodeling of the heart, such as angiotensin-converting enzyme inhibitors, sartans or aldosterone receptor antagonists, may be particularly beneficial in patients with increased concentrations of these markers after MI. Importantly, it has been demonstrated that the prevention of unfavourable myocardial remodeling due to eplerenone is more strongly expressed in patients with high sST-2 concentration [41]. In addition, there are reports that it is possible to inhibit the progression of heart failure by pharmacological or genetic blocking of biomarkers, which gives an additional perspective on the use of metabolic pathways of these proteins in the therapy of heart failure [7, 42]. There are also data showing better response to statin therapy in patients with lower Gal-3 concentrations [17].

Summary

The need to extend diagnostic algorithms has initiated many studies on new markers. Numerous studies and publications present the possibility of comprehensive use of Gal-3 and ST-2 protein. It has been shown that Gal-3 and ST-2 protein, due to their connection with fibrosing processes, may turn out to be the key markers in patients with coronary artery disease and post MI. It is suggested that Gal-3 in the initial stages after MI contributes to proper tissue repair, but over time its excessive activation leads to unfavourable remodeling of the left ventricle. The ST-2 protein can provide valuable predictive information on the risk of developing heart failure. In addition, there are reports of the use of new biomarkers to evaluate prognosis after TAVI treatment or to predict the benefits of resynchronization therapy. Pharmacological or genetic potential for interference in the pathways of both molecules is being studied. However, due to small groups of patients and relatively short observation time, conclusions from these studies are limited.

Conflict of interest

Authors declare no conflict of interest.

Streszczenie

Istnieje wiele markerów oceny ryzyka chorób sercowo-naczyniowych. Wciąż poszukuje się nowych czułych i specyficznych biomarkerów, które mogłyby pomóc w stratyfikacji ryzyka zarówno wśród populacji zdrowej, jak i obciążonej chorobami sercowo-naczyniowymi. Galektyna 3 oraz białko ST-2 wydają się być niezwykle obiecującym wskaźnikami, niemniej jednak potrzeba dalszych badań nad tymi cząsteczkami do poznania ich pełnej wartości diagnostyczno-prognostycznej. W pracy prezentujemy badania i publikacje przedstawiające możliwość wszechstronnego wykorzystania obu biomarkerów, zwłaszcza w chorobie wieńcowej. Galektyna 3 oraz białko ST-2, poprzez swój związek z procesami włóknienia, mogą okazać się kluczowymi markerami u pacjentów z chorobą wieńcową oraz po zawale serca.

Słowa kluczowe: białko ST-2, choroby sercowo-naczyniowe, choroba wieńcowa, galektyna 3, remodeling, zawał serca

Folia Cardiologica 2019; 14, 1: 60–66

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