Neuregulin-4, an Adipokine, as a Residual Risk Factor of Atherosclerotic Coronary Artery Disease

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Over the past 30 years, treatment strategies for classical risk factors of coronary artery diseases (CAD) such as hypertension, hypercholesterolemia, and diabetes mellitus have advanced remarkably. However, ischemic heart diseases still remain the leading cause of heart failure and cardiovascular death worldwide, and identification and treatment of the residual risk factors is essential.¹⁾ Adipokines are gaining attention as residual risk factor candidates and as novel treatment targets of CAD. The association between adipokines such as interleukin-6, adiponectin, leptin, and tumor necrosis factor alpha and CAD is being studied. In addition, the drugs that affect the adipokines are also being examined as potential therapeutics.²⁻⁸⁾

A recently identified adipokine, neuregulin-4 (Nrg4), is one of the four neuregulin family proteins: cell-cell signaling proteins that possess an EGF-like domain and bind to the ErbB family tyrosine kinase receptors.⁹⁾ Nrg4 was first identified as a neuregulin family protein enriched in the pancreas,¹⁰⁾ but recently Rosell, *et al.* reported that Nrg4 is highly expressed in brown adipose tissues (BAT) as an adipokine; its role in atherosclerosis has been gaining attention.¹¹⁾ Jiang, *et al.* showed that serum Nrg4 levels were lower in patients with metabolic syndromes, and Cai, *et al.* showed that serum Nrg4 levels inversely correlate with carotid intima-media thickness.^{12,13)}

In their analyses, the serum Nrg4 level did not correlate with age, body mass index, low density lipoprotein cholesterol levels, high-sensitivity C-reactive protein, or glycosylated hemoglobin A1c, but did correlate with the SYNTAX score, suggesting that serum Nrg4 is a predictor of CAD severity. ROC curve analysis revealed that serum Nrg4 levels had both high sensitivity and specificity for the identification of patients with severe CAD. The present study suggested the potential of Nrg4 as a residual risk factor and as a novel therapeutic target for CAD.¹⁴⁾

However, two important questions remain to be answered in order to understand the effect of serum Nrg4 on CAD: (1) is there any causal relationship between the increased level of serum Nrg4 and the presence and the severity of CAD; and (2) what accounts for the changes in serum Nrg4 levels and what is the possible intervention to alter the levels?

Although the present study and the aforementioned population studies only show an association between Nrg4 and CAD with no information on the causality, data from a rodent model suggest that serum Nrg4 affects the formation of atherosclerosis. Clement, *et al.* showed that ErbB4, the receptor of Nrg4, increased dramatically in the endothelium of a rat carotid artery injury model.¹⁵⁾ In the same study, treatment with neuregulin-1 (a member of the neuregulin family proteins which can also activate ErbB4) attenuated neointima formation.¹⁵⁾ Signaling via ErbB4 tyrosine kinase receptors shows an anti-apoptotic effect via stimulation of the Akt/PI3K pathway,¹⁶⁾ which reportedly inhibits endothelial cell apoptosis and prevents the progression of atherosclerosis.^{17,18)} These indirect findings are not conclusive, however, and further human cohort studies and biological studies are therefore required.

The mechanisms of the regulation of serum Nrg4 levels and the possible therapeutics to increase that level are unknown. Nrg4 is highly expressed in BAT, and the amino acid sequence of Nrg4 codes a transmembrane domain and an EGF-like domain, with a putative proteolytic cleavage site in between, suggesting that the cleavage is required for the formation of mature secretory Nrg4.¹⁰⁾

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In this issue of International Heart Journal, Tian, *et al.* have expanded these previous findings to include the association between serum Nrg4 levels and the presence and complexity of CAD.¹⁴⁾ The authors reported for the first time that serum Nrg4 levels were significantly lower in patients with CAD. Logistic regression analysis revealed that serum Nrg4 level was a predictor for the presence of CAD, independent of the patients' blood pressure, low density lipoprotein cholesterol levels, and smoking status, thus indicating serum Nrg4 as a possible residual risk factor. They also showed that a higher SYNTAX score was associated with lower serum Nrg4 levels among

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Figure A possible model of the effect of Nrg-4 on coronary artery disease. Alterations in the amount of brown adipose tissue, the expression of Nrg-4 within the brown adipose tissue, or the secretion of Nrg-4 from the adipose tissue may contribute to the decreased serum Nrg-4 levels, resulting in increased endothelial cell apoptosis and coronary artery disease. Nrg-4, Neuregulin-4.

The key determinant factor of serum Nrg4 levels may be the amount of BAT, the level of Nrg4 expression within the BAT, the proteolytic cleavage and secretion of the Nrg4 from the BAT, or the removal of Nrg4 from systemic circulation, and drugs that can modulate each factor have the potential to increase serum Nrg4 levels (Figure).

As a drug used to increase the amount of BAT, the PPAR γ agonist rosiglitazone has been identified;¹⁹⁾ the drug also reportedly restores Nrg4 expression in adipocytes.²⁰⁾ However, although there are many conflicting results, the drug has safety concerns especially for congestive heart failure patients and thus its use in patients with CAD may require caution.²¹⁾ Recently, a cyclin-dependent kinase inhibitor, roscovitine, was reported to induce browning of the adipose tissue, enhance energy expenditure, and prevent diet-induced obesity.²²⁾ Phase 2 clinical studies have been completed on roscovitine for nasopharyngeal and non-small cell lung cancer, and human trials on non-cancer diseases such as rheumatoid arthritis are ongoing.^{23,24)} The medical community is awaiting increased research into CAD.

As a drug to increase the level of Nrg4 expression within BAT, beta 3-adrenoceptor (B3AR) agonists have been reported.²⁵⁾ B3AR agonists were investigated as potential anti-obesity drugs in the 1990s, but the low selectivity and bioavailability of the old B3AR agonists hindered the expansion of the research.²⁶⁾ The recently approved B3AR agonist mirabegaron achieved satisfactory bioavailability with high specificity; it reportedly activates human BAT thus raising expectations for future treatment.²⁷⁾

The present study provides important knowledge about the association between serum Nrg4 levels and CAD.¹⁴⁾ Further research on this adipokine may expand our understanding of the pathophysiology of atherosclerosis and lead to the development of new therapeutics.

Disclosures

Conflicts of interest: None.

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