Letter to editor

Does the obesity-associated adipokine leucine-rich alpha2-glycoprotein 1 (LRG1) have a regulatory role of the skeletal muscle adaptive response to exercise?

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Dear Editor-in-Chief

Overweight and obesity are considered as the most important lifestyle-related diseases today such that they are known as the fifth leading causes of death worldwide according to the published statistics. Moreover, as previous studies have shown, low-grade chronic inflammation is among the symptoms of these diseases and plays a key role in the pathogenesis of various physical problems and chronic diseases, such as cancer, diabetes, metabolic syndrome, cardiovascular, and neurodegenerative diseases (Safaei et al., 2021). Meanwhile, new evidence suggests that leucine-rich α 2-glycoprotein 1 (LRG1) proinflammatory factor, an important upstream signaling pathway of transforming growth factor-β (TGF-β), will cause several pathological processes (Zou et al., 2022). In other words, it can be stated that LRG1, alone or in combination with other known factors, is considered as a potential biomarker for inflammation and obesity. There is a positive relationship between high levels of LRG1 and obesity, while low levels of plasma LRG1 predict weight loss in surgery for obesity and metabolic diseases (Pek et al., 2018). Investigation of the importance and the relationship of this issue in a broad study on 2,058 patients with type 2 diabetes showed that higher plasma LRG1 levels in women than men have a significant relationship with several risk factors for cardiovascular disease, namely arterial stiffness, endothelial dysfunction, systolic blood pressure, obesity, kidney disease, and high-sensitivity C-reactive protein (Pek et al., 2018; Zou et al., 2022). A recent 8-year longitudinal study also found that pigment epithelial-derived factor and plasma LRG1 mediated the inverse relationship between skeletal muscle mass and chronic kidney disease progression in patients with type 2 diabetes (Low et al., 2021). In other words, there is a positive correlation between high LRG1 level-s in blood serum and adipose stores and high levels of body-mass-index (BMI), visceral adipose tissue, and waist circumference of obese people. According to these results and laboratory observations, LRG1 has been assumed to increase fat accumulation via suppression of fatty acids catabolism and inducing lipid biosynthesis through sterol regulatory element-binding transcription factor 1 activation or may enable hyperglycemia by decreasing expression of insulin receptor substrates (IRS1 and IRS2) (He et al., 2021).

On the other hand, consistent with the findings of studies showing the high serum levels of LRG1, it is possible that LRG1 binds preferentially to liver cells. With this assumption, LRG1 is considered a new adipokine that can play a role in obesity conditions by regulating an almost unique cross-talk between adipose tissue and the liver. More broad research is required to know whether LRG1 also exerts metabolic functions in physiological circumstances or not. However, the results of a study on LRG1 knockout mice with a high-fat diet revealed weight loss, smaller fat cell size, and preservation of brown adipose tissue in this type of mice. In other words, an increase in LRG1 gene expression during the process of fat lipogenesis can play an important role in regulating energy homeostasis (He et al., 2021; MacCannell et al., 2021). However, changing lifestyle by performing regular physical activity and a balanced diet have been introduced as a useful solution to prevent obesity. In this regard, a recent study on the elderly with an average BMI of 34 ± 1 kg / m2 showed that exercise combined with diet resulted in an 8-10 % weight loss in these individuals, indicating the possibility that molecular changes in peroxisome proliferator-activated receptor γ (PPARγ) coactivator 1α (PGC-1α) pathway can help transport fat and oxidize it in the skeletal muscles of older and obese people and in some ways regulate insulin resistance (Mulya et al., 2017).

Previous research studies have referred to the key role of PGC-1α in regulating mitochondrial function and helping regulate cellular energy status by enabling cellular energy in conditions

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when the body needs energy, such as fasting, performing exercise activities, or inhibiting it when the body has enough energy available. However, the evidence obtained regarding the role of PGC-1α and its relationship with LRG1 gene expression in obesity therapy showed that LRG1 expression in white adipose tissue reduced in mice model of insulin - resistant type II diabetes and obesity following treatment with PPARγ agonists (Muise et al., 2008). Moreover, evidence regarding the positive effects of exercise activity and the role of PGC-1α showed that probably five proteins, including interleukin 15 (IL-15), fibronectin type III domain- containing protein 5 (FNDC5), vascular endothelial growth factor B (VEGF-B), LRG1, and tissue inhibitor of metalloproteinase 4 (TIMP4), secreted in skeletal muscles, increase following endurance exercise activity and contribute to longevity as well (Boström et al., 2012).

Considering the evidence presented, LRG1 seems to play a key role in the pathogenesis of obesity. However, more broad research is required to better understand its relationship with other transcription factors, vital signaling pathways in this process, as well as the important effect of type, intensity, and duration of exercise activity, and type of diet in regulating its expression and its regulatory role in cross-talk with other organs to prevent obesity (Yang et al., 2021).

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