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MicroRNAs in muscle wasting and cachexia induced by heart failure

Yihua Bei and Junjie Xiao

We read with great interest the Review by von Haehling *et al.* (Muscle wasting and cachexia in heart failure: mechanisms and therapies. *Nat. Rev. Cardiol.* **14**, 323–341; 2017)[1], which discussed the pathophysiological mechanisms of muscle wasting and cachexia in heart failure (HF) and outlined therapeutic approaches. Specifically, combined therapy including nutrition counselling, exercise training, and drug treatment after standard HF therapy was recommended for patients with HF and body wasting. The involvement of microRNAs (miRNAs or miRs) in the regulation of muscle atrophy and HF has been increasingly demonstrated. We wish to highlight some important findings about the essential roles of miRNAs in this field, which might pave the way for further investigation of miRNA-based therapeutic targets for muscle wasting and cachexia in HF.

HF is the end stage of many cardiovascular diseases associated with cardiomyocyte hypertrophy, apoptosis, angiogenesis, and cardiac fibrosis; each of these pathophysiological processes can be promoted or impaired by miRNAs[2]. miRNAs — a large group of short, non-coding RNAs that regulate gene expression post-transcriptionally — are also linked to epigenetic modifications to control gene expression in cardiac hypertrophy and failure[3]. Of note, some muscle-specific miRNAs (also called myomiRs), such as miR-1 and miR-133, were reported to have roles in both cardiac hypertrophy and muscle atrophy[4]. Interestingly, miR-21, which critically contributes to cardiac fibrosis, has been shown to promote muscle wasting[5,6]. Moreover, miR-23a, which contributes to cardiac hypertrophy, was found to protect against muscle atrophy by targeting E3 ubiquitin-protein ligase TRIM63 (also known as MURF1)[7,8]. These studies indicate that miRNAs might have concordant or discordant roles in the regulation of HF and muscle atrophy. However, current knowledge about the role of miRNAs in muscle wasting and cachexia in HF is very limited and needs further investigation.

In addition to HF, the loss of skeletal muscle mass and strength can be related to a variety of diseases, such as denervation, physical disability, fasting, ageing, and cancer. miR-29b has been reported to have a central role in muscle atrophy[9]. miR-29b is ubiquitously upregulated in various models of muscle atrophy induced by denervation, dexamethasone, fasting, cancer cachexia, or ageing. miR-29b promotes muscle atrophy, whereas reducing miR-29b levels attenuates muscle atrophy. Importantly, the genes that encode insulin-like growth factor I (IGF1) and phosphatidylinositol 3-kinase regulatory subunit α (PI3K p85α) were identified as two targets of miR-29b. miR-29b was shown to promote muscle atrophy by inactivating IGF1–PI3K–Akt–mTOR signalling, which is an essential molecular pathway involved in protein synthesis. This study provides a potential common therapeutic target for multiple types of muscle atrophy. Of note, miR-29b is also induced in ageing-related muscle atrophy, and ageing is a major risk factor for HF[10]. Therefore, the roles of altered miRNA levels (such as those of miR-29b) warrant further investigation in muscle wasting and cachexia in HF.

In summary, a deep understanding of the potential roles of miRNAs in the regulation of muscle wasting and cachexia in HF might provide novel therapeutic targets to counteract muscle loss and weakness for patients with HF.

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Competing interests statement
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