Letter to editor

# Exercise and macrophage phenotype switch: The role of myokine meteorin-like protein (METRNL)

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## Dear Editor-in-Chief

Originally, macrophages are known for the critical role of phagocytosis in innate immunity (Yan & Hansson, 2007). They have also been shown to play crucial roles in the homeostasis of white adipose tissue (WAT) and skeletal muscle (SKM) tissue (Baht et al., 2020; Rao et al., 2014). Macrophage plasticity is an important hallmark enabling them to respond to altered settings (Shapouri-Moghaddam et al., 2018). In response to those changing environments, macrophages demonstrate different polarizations of the classic/proinflammatory M1 phenotype and an alternative/anti-inflammatory M2 phenotype (Shapouri-Moghaddam et al., 2018). Obesity, as an adipose tissue's milieu-altering stimulant, shifts the macrophage phenotype to the pro-inflammatory M1 phenotype, with the resultant consequences of inflamed adipose tissue and insulin resistance, showing that adipose tissue macrophages (ATMs) are central players in adipose tissue homeostasis (Goh, Goh, & Abbasi, 2016). On the other hand, exercise has been well documented to reduce obesity-induced adipose tissue (AT) inflammation. Exercise-induced mechanisms through which AT inflammation is attenuated, include a combination of: i) a decrease in inflammatory adipokines production, ii) a reduction of toll-like receptors (TLR2 and TLR4) expression in immune cells, and iii) an increase in the production of muscle-secreted factors called myokines (Abbasi et al., 2014; Pedersen & Febbraio, 2008). The latter mechanism, muscle-fat crosstalk, is mediated by myokines to deliver exercise-induced health benefits (Pedersen & Febbraio, 2008). Basically, exercise, in a tissue-specific manner, upregulates lipid oxidation-related genes and proteins which in turn decrease oxidative stress and pro-inflammatory cytokine production in the inflamed AT (Ruschke et al., 2010). In parallel, exercise-induced muscle contraction triggers the production of genes and proteins in SKM that are responsible for the secretion of molecules called myokines to mediate the beneficial effects of exercise (Pedersen & Febbraio, 2008). Meterorin-like protein (Metrnl) is a newly-identified adipomyokine with immune-regulatory hallmarks (Rao et al., 2014). Metrnl was originally identified as a myokine with immune regulatory functions in AT (Rao et al., 2014). Exercise-induced increases in blood Metrnl levels act as a signaling molecule to recruit eosinophils into AT, driving the M2-phenotype of ATMs, and finally resulting in the browning of white adipose tissue (BWT) (Rao et al., 2014). Metrnl has been shown to upregulate the production of type 2 immunity anti-inflammatory cytokines, IL-4 and IL-13 which in turn activate ATM's M2 phenotype in a STAT6-dependent pathway in macrophages in animal models (Rao et al., 2014). Exercise-induced Metrnl is correlated with its increased blood levels which is associated with elevated whole-body energy expenditure via stimulating the thermogenesis process in AT (Rao et al., 2014). Based on this evidence, Metrnl-mediated ATMs phenotype shift is related to improved metabolic health in obesity, suggesting Metrnl as a possible therapeutic agent in metabolic challenges.

In the study of Rao et al., given the ability of Metrnl in recruiting type 2 immunity, and that type II immunity has characteristics in repairing processes like those in damaged SKM, it was hypothesized that Metrnl might also play roles in regenerating damaged SKM. In this regard, in a recently published study by Baht et al., Metrnl was described as a necessary regulator for SKM regeneration process (Baht et al., 2020). Baht et al's study's finding was that Metrnl is induced upon SKM-damaging exercise. In that study, SKM-derived Metrnl was delineated as dispensable for the regeneration of damaged SKM, whereas macrophage-derived Metrnl was shown as a critical coordinator for SKM regeneration (Baht et al., 2020). Macrophage-derived Metrnl, in an auto-/paracrine manner, activates STAT3 which in turn promotes an anti-inflammatory function and induction of insulin-like growth factor 1 (IGF-1), which activates muscle pro-

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-genitors to help myogenesis (Baht et al., 2020). Similar to its actions in AT, Metrnl exerts its physiological functions through macrophage accretion and phenotypical shift in SKM. Of note, in the study of Rao et al. Metrnl was established as a molecule that is selectively expressed in different tissues based on physiologic stimuli with being expressed in AT upon cold exposure and in SKM upon exercise (Rao et al., 2014). With regard to this, in the study of Baht et al. it was shown that there was no Metrnl expression in myogenic cells after injury and that mice with Metrnl silenced in myofibers exhibited a normal phenotype in terms of muscle regeneration while macrophages were the main Metrnl-secreting cells in SKM injury (Baht et al., 2020). There are a handful of studies reporting Metrnl responsiveness to SKM-damaging exercise protocols like unaccustomed resistance exercise (Baht et al., 2020; Rao et al., 2014), downhill running exercise (Alizadeh & Alizadeh, 2021; Rao et al., 2014) in both animal and human subjects. These observations prompt questions regarding the molecular mechanisms that control the selective expression of Metrnl molecule by different cell types according to tissue homeostasis: myofibers after exercise versus macrophages after damage.

In summary, this letter addressed two outstanding studies of Rao et al., and Baht et al., describing Metrnl mechanisms of action in both AT and SKM physiology. Metrnl actions are mediated via macrophage phenotype switch (MPS) in AT and SKM. In AT, MPS leads to BWT, while, in SKM, Metrnl-mediated MPS results in muscle regeneration, representing Metrnl as a new therapeutic target for inflammatory diseases. What remains unknown, in addition, is that these findings (BWT and SKM regeneration) observed in transgenic animal models still need to be verified in humans. In relation to SKM regeneration, the good news is that Metrnl is induced in damaged human SKM, suggesting that Metrnl is responsive to exercise-induced SKM damage. However, the critical question is which stimuli trigger Metrnl expression in macrophages and whether also other exercise-induced challenges that could induce Metrnl. These new findings raise the question of whether Metrnl could be employed to reprogram pro-inflammatory into anti-inflammatory macrophages and, as such, serves as a new therapeutic target for inflammatory diseases not directly related to muscle repair. What would be useful to speculate, is the type, duration and intensity of exercise that can modulate the release and uptake of Metrnl, possibly also affecting the macrophage polarization state further downstream.

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