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Dual role of Metrnl: exercise-induced benefits and potential cancer implications

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ABSTRACT

Metrnl (Meteorin-like), a protein elevated by exercise, supports metabolic regulation, inflammation reduction and glucose homeostasis. While exercise is a cornerstone of cancer prevention and management, recent findings suggest that Metrnl plays a dual role, potentially impairing T-cell function in the tumor microenvironment. This commentary explores the interplay between Metrnl's systemic benefits and its local immunosuppressive effects in cancer. Despite these concerns, exercise remains broadly advantageous for patients with cancer, though further research is essential to understand Metrnl's context-specific impacts.

INTRODUCTION

Exercise is a proven ally in cancer prevention and treatment, enhancing immune surveillance, curbing inflammation and optimizing metabolism.[1] These benefits are partly mediated by myokines—cytokines secreted by skeletal muscles during activity.[2] Meteorin-like protein (Metrnl) emerges as a complex player, promoting metabolic health,[3] while raising questions about its role in cancer.[4] In the tumor microenvironment (TME), Metrnl hinders antitumor immunity,[4] creating a potential paradox. This commentary examines exercise-induced Metrnl's dual effects, aiming to guide healthcare professionals and researchers toward refining exercise strategies in oncology.

BACKGROUND ON METRNL

Metrnl, or Cometin, Subfatin, is a secreted adipomyokine expressed in tissues such as the liver, heart, skeletal muscle, adipose tissue, skin, mucosal tissues and activated macrophages.[5] Its presence in barrier tissues such as skin and mucosa suggests roles in tissue integrity and immune surveillance at environmental interfaces.[6] Functioning as both a metabolic regulator and immunoregulatory cytokine, Metrnl shapes innate and adaptive immunity.[7] In activated macrophages, Metrnl production is induced by cytokines such as tumor necrosis factor alpha (TNF-α) and interleukin (IL)-4, while interferon-γ suppresses it, highlighting its influence on inflammation.[6] Studies using Metrnl knockout mice underscore its importance, showing that its absence disrupts cytokine balance and increases sepsis vulnerability.[6]

EXERCISE AND METRNL INDUCTION

Physical activity significantly boosts Metrnl expression in skeletal muscle.[3] Both acute and chronic exercise elevate Metrnl levels, driving metabolic benefits such as increased energy expenditure, enhanced glucose tolerance and resistance to insulin dysfunction.[3] Metrnl inhibits the NLRP3 (nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3) inflammasome—a key inflammation trigger—reducing proinflammatory cytokines, such as IL-1β and IL-18. It also promotes an anti-inflammatory macrophage phenotype, supporting muscle repair and cardiometabolic health.[8]

METRNL'S ROLE IN CANCER

Recent research reveals a concerning facet of Metrnl in cancer. A 2024 study from Johns Hopkins University found that Metrnl in the TME depletes energy from T cells—crucial immune cells for tumor elimination—compromising their effectiveness.[4] This suggests that exercise-induced Metrnl might inadvertently aid tumor progression, prompting a closer look at its role in cancer contexts.

EXERCISE IN PATIENTS WITH CANCER: GENERAL BENEFITS

Despite Metrnl's potential drawbacks, exercise consistently benefits patients with cancer. Systematic review and meta-analysis studies show that it reduces recurrence risk, lowers mortality and improves quality of life.[9 10] Exercise also creates a 'metabolic shield' in distant organs, limiting nutrient availability to tumors, potentially reducing metastasis and enhancing immune cell activity.[11]

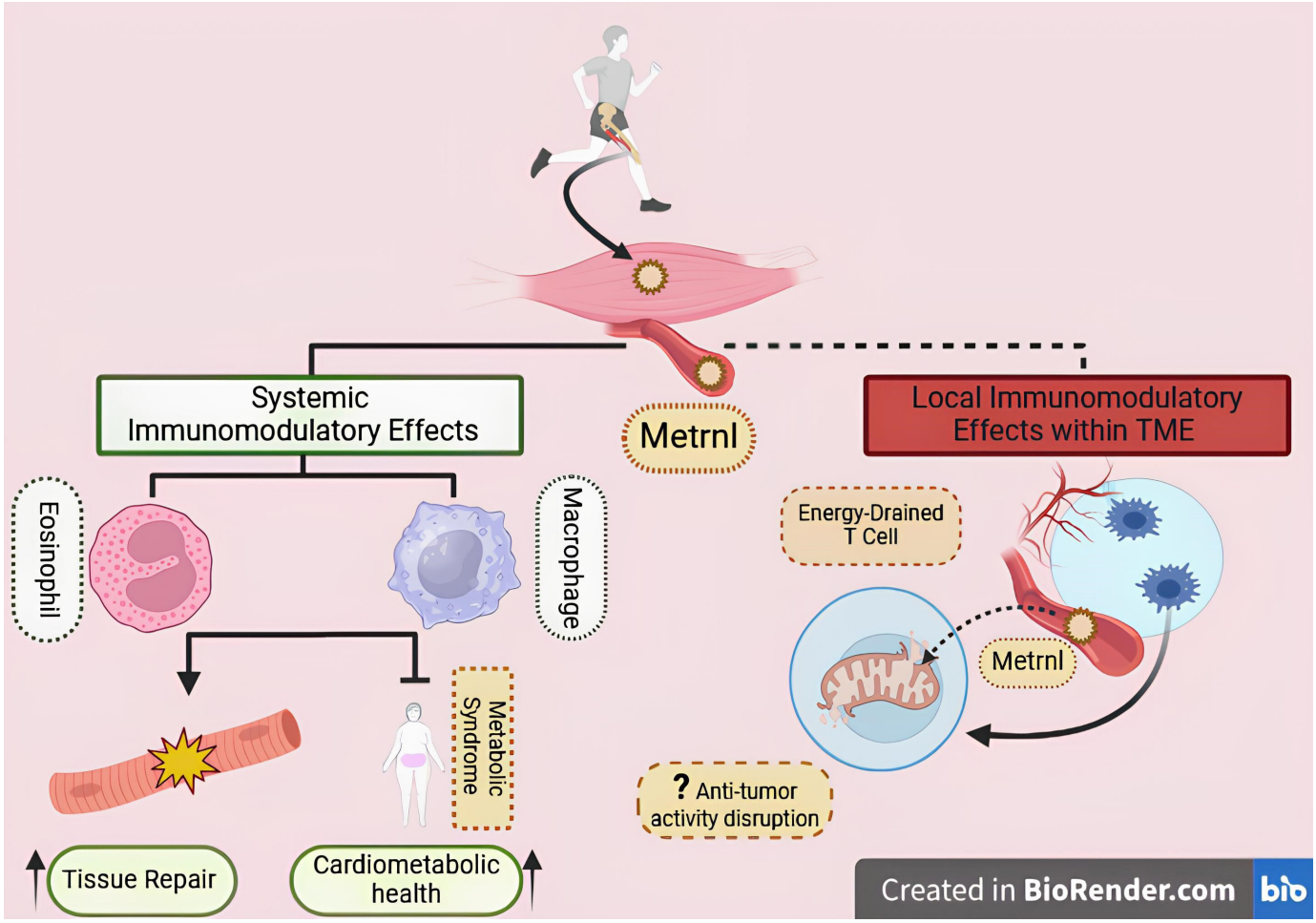

Figure 1 Differential roles of exercise-induced matrnl in systmetic and tumor microenvironment (TME) contexts. This diagram illustrates the systemic benefits of Metrnl induced by exercise, including improved glucose tolerance, reduced inflammation, and metabolic regulation. Conversely, within the TME, Metrnl may hinder anti-tumor immunity by depleting T cell energy, potentially facilitating tumor progression. The question mark indicates uncertainty regarding whether exercise-induced Metrnl affects TME levels or is confined to systemic circulation. Further research is needed to clarify this complexity. This image was created using BioRender software. →: Inducer; Dashed arrow(s) indicate potential effects.

POTENTIAL CONFLICT: EXERCISE-INDUCED METRNL AND CANCER

Exercise's induction of Metrnl introduces a tension: its systemic benefits contrast with its potential to impair T cells in the TME. Yet, no direct evidence links exercise-induced Metrnl to elevated TME levels sufficient to disrupt immunity. Systemic advantages—such as reduced inflammation and improved metabolism—likely outweigh localized risks. However, the absence of studies measuring Metrnl in exercising patients with cancer leaves this relationship unclear.

DISCUSSION AND IMPLICATIONS

Metrnl's dual nature—delivering systemic benefits while potentially compromising immunity in the TME—presents a complex challenge for cancer care. Exercise's well-documented positive effects on patients with cancer[11] suggest that Metrnl's metabolic advantages, such as enhanced glucose tolerance and reduced inflammation,[3] may overshadow its immunosuppressive tendencies. However, understanding how Metrnl levels change in different contexts—specifically during exercise versus within the TME—is critical to resolving this tension.

During exercise, Metrnl levels rise systemically, primarily driven by its release from skeletal muscle and adipose tissue.[3] This increase is rapid and tied to physical activity's intensity and duration, contributing to widespread metabolic and anti-inflammatory effects.[3] In contrast, within the TME, Metrnl levels appear to be locally elevated, not necessarily as a direct result of exercise but through secretion by immune cells such as activated macrophages or possibly tumor cells themselves.[4] This localized production may persist or intensify as part of the tumor's immune evasion strategy, depleting T-cell energy and impairing antitumor responses.[4] The source and regulation of Metrnl thus differ: exercise induces a transient, systemic spike, whereas TME levels reflect a sustained, context-specific accumulation influenced by tumor dynamics (figure 1).

These distinct patterns raise important questions. Exercise-induced Metrnl, circulating broadly, may not reach concentrations in the TME sufficient to mirror the immunosuppressive effects observed locally. Alternatively, if systemic Metrnl does contribute to TME levels, its benefits elsewhere (eg, reduced systemic inflammation) might still outweigh this drawback. The 2024 Johns Hopkins findings highlight Metrnl's detrimental role in tumors[4] but do not directly link it to exercise, leaving open the possibility that TME-specific Metrnl is a tumor-driven phenomenon rather than an exercise-related one (figure 1). Future studies should measure Metrnl levels in both systemic circulation and the TME of exercising patients with cancer, alongside assessing immune function, to determine whether exercise exacerbates or mitigates T-cell dysfunction. Such research could reveal whether exercise regimens need adjustment—perhaps by intensity or type—to optimize Metrnl's beneficial effects while minimizing any tumor-related risks.

The broader implications are clear: while exercise remains a net positive, the differential behavior of Metrnl across contexts demands a nuanced approach. Tailoring exercise prescriptions for patients with cancer could hinge on understanding these dynamics, ensuring that systemic benefits are maximized without inadvertently fueling TME immunosuppression.

CONCLUSION

Metrnl, elevated by exercise, offers metabolic and anti-inflammatory benefits but may hinder T-cell function in the TME. Despite this, exercise retains a net positive effect on patients with cancer. The differing dynamics of Metrnl levels—systemic spikes from exercise versus localized accumulation in the TME—highlight a critical research gap. Targeted studies are essential to refine exercise recommendations, ensuring that patients with cancer gain maximum benefits while addressing Metrnl's complex role.

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