Editorial

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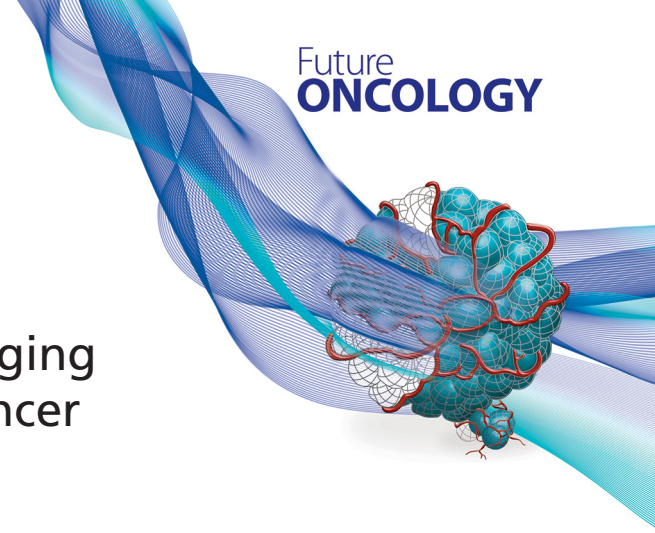

Exercise-induced myokines as emerging therapeutic agents in colorectal cancer prevention and treatment

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"There is emerging evidence that myokines may have significant antineoplastic benefits and may represent a major mechanism through which the salutary benefits of exercise are transduced."

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Colorectal cancer (CRC) remains the second leading cause of cancer deaths in western countries underscoring the need for more effective preventive and therapeutic strategies. The risk of CRC development can be attributed to both genetic and exogenous (diet, obesity and diabetes, etc.) factors. Importantly, it is estimated that lifestyle factors may be responsible for much of the CRC risk (~30–60%) [1]. Of these, exercise remains one of the most common and practical modifiable factors with approximately 45% of Americans currently being classified as sedentary (not meeting the recommended 150 minutes/week of moderate-to-vigorous physical activity). This has been implicated in a variety of cancers as noted in a study of 1.44 million adult participants who were dichotomized into those with high versus low leisure time physical activity. The higher exercise group had a decreased risk of colon (hazard ratio: 0.84; 95% CI: 0.77–0.91) and rectal cancer (hazard ratio: 0.87; 95% CI: 0.80–0.95) with comparable effects observed in 12 other cancers including esophageal adenocarcinoma, liver, lung, kidney, gastric cardia, endometrial, myeloid leukemia, myeloma, head and neck, breast and bladder [2].

There is a large body of evidence that has confirmed that physical activity reduces CRC risk by about 20–25% in both men and women in a dose-dependent manner [3]. This effect seems equivalent for both CRCs in the proximal CRC with a relative risk (RR; RR = 0.73: 95% CI: 0.66–0.81) and distal (RR = 0.74; 95% CI: 0.68–0.80) despite significant biological differences in these subsites [4]. Physical activity is associated with a decreased occurrence of premalignant lesions (risk reduction for adenomas and advanced adenomas of approximately 15 and 35%, respectively) [3]. There is unequivocal data showing physical activity/exercise exerts a protective effect independent of co-segregating variables such as obesity and diabetes [3]. Moreover, in a randomized controlled trial, moderate-to-vigorous intensity exercise intervention was shown to modestly but significantly reduce the colon crypt cell proliferation patterns in men who exercised at least 250 min/week [5].

Along with the cancer preventive benefit, there is emerging evidence that exercise may actually improve survival in patients who have already developed CRC [6]. Physical activity significantly decreased cancer recurrence and CRC-related deaths [7]. There is significant association between prediagnostic physical activity and CRC prognosis after diagnosis in terms of overall, CRC-specific, recurrence-free and disease-free survival [6]. Park *et al.* noted that exercise and low body-fat mass were significantly correlated with lower rates of colorectal polyp recurrence in the surveillance of CRC survivors [8]. Another meta-analysis reported that physical activity after the diagnosis of CRC was associated with a marked decrease in the pooled relative risk in mortality with a CRC specific mortality of 0.77 (95% CI: 0.63–0.94) and total mortality of 0.71 (95% CI: 0.63–0.81) [9]. Furthermore, exercise therapy may be beneficial for CRC patients during adjuvant treatment. Specific guidelines for physical activity for cancer survivors have been recommended given these wide-ranging benefits.

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The prescription of exercise as an adjuvant therapy has been reported by prospective cohort studies to reduce the risk of recurrence and death among colon cancer survivors [7,10]. The dose-response nature was nicely demonstrated in the randomized COURAGE exercise trial in which frequent moderate-intensity aerobic exercise elicited favorable prognostic biomarker alterations in patients recently treated for stage I–III colon cancer [10]. However, concerns still remain regarding the feasibility, tolerability and efficacy of compliance of recommended exercise regime in cancer patients suffering from cancer and chemotherapy-related fatigue. Furthermore, compliance with lifestyle modifications in the population has been relatively dismal highlighting the need to develop pharmacological agents that provide similar benefit. For this, understanding the biology of exercise-mediated benefit is critical.

Biologically, exercise appears to impact on numerous of the Hanahan and Weinberg's 'hallmarks' of cancer including resisting cell death, sustaining proliferative signaling, evading growth suppressors, activating invasion and metastasis, enhancing replicative mortality enhancing angiogenesis, reprogramming energy metabolism and evading immune destruction [3]. There is a myriad of putative molecular mechanisms (metabolic changes, modulating insulin/insulin growth factor signaling, immune alterations and epinephrine release, etc.). While the mechanisms of exercise effect are undoubtedly pleotropic, several lines of evidence suggest that skeletal muscle may have a role. For instance, in a prospective cohort trial with an average of 18.8 years follow-up, those with the lowest and middle third of muscle strength had a higher risk of cancer development when compared with the highest third (1.59 and 1.70 respectively) [11]. From a therapeutic perspective, a provocative report suggested that preoperative psoas muscle strength was a powerful predictor of survival for patients undergoing surgical pancreatic cancer [12]. From a mechanistic perspective, there are intriguing data that suggest skeletal muscle is an endocrine organ secreting cytokines in response to contraction (termed myokines) which may transduce the numerous antineoplastic effects [3].

The role of myokines in biology was pioneered in a series of reports from Pedersen and colleagues. This started with the classic discovery of cytokine IL6, which is released from skeletal muscle during exercise [13]. They showed that breast cancer cells treated with serum collected from animal post exercise caused significant decrease in proliferation and increased apoptosis leading to abrogation of tumor growth [14]. Their later work has reported crosstalk between myokines and immune cells leading to the coining of the term 'diseasome' of physical activity.

In the past few years, there has been an explosion in the number of cytokines secreted by contracting muscles (termed 'myokinome') that have been identified. Currently, there are more than 3000 myokines reported [15] with several of them having potential anticancer benefit. In an experimental model of colon carcinogenesis, a novel myokine *SPARC* has been shown to transduce the protective effects of exercise [16]. In addition, myokine irisin (*FNDC5*) has been shown to decrease breast cancer aggressiveness and also enhance chemotherapy [17]. Furthermore, a recent study, featured in the *New England Journal of Medicine* indicated that IL-6 had an antineoplastic benefit by targeting immune cells (NK cells) providing another putative mechanism of action [18]. In prostate cancer, there is speculation that myokines may interact with adipokines thereby potentially amplifying its effect. Additional studies using animal models of CRC and melanoma suggest that myokines manifest an anticancer effect *in vivo* [16]. Thus myokines represent a promising target for exercise induced antineoplastic effect. The mechanisms of exercise and cancer are likely pleotropic but may inform about potentially novel drug targets.

The dissection of the precise myokine(s) involved through analysis of blood from animal or human studies is remarkably difficult given the challenges of analyzing the circulating proteome. Furthermore, many members of the myokinome have been reported to have antagonistic effects (e.g., some considered pro-neoplastic and others antineoplastic). Thus, unraveling the molecular interplay between myokines and identifying the potentially therapeutic ones necessitates a simplified system. Our laboratory has adapted the *in vitro* exercise platform (myotubules stimulated with C-Pace system) [19] and used it for the application of discovering specific myokines (individual or combination) which may have therapeutic effects. Our initial focus has been on synergism of myokines with chemotherapy in CRC [20]. Furthermore, we noted that myokines by itself exhibited some antineoplastic effect. This platform approach has implications for a variety of cancers along with non-neoplastic conditions which have been reported to benefit from exercise (obesity, atherosclerosis, diabetes and fatty liver, etc.). Importantly, given the paradigm for chemotherapy is combination (e.g., FOLFOX or FOLFIRI in CRC), the best approach may be a combination of myokines probably with conventional cytotoxic chemotherapy. Furthermore, since cancer is a heterogeneous disease, it is likely that myokines may be somewhat specific for cancer type or at least have similarities between different cancer types that have the same molecular drivers (e.g., Ras signaling).

Therefore, these novel cell culture approaches may give a way to translate the epidemiological/biological insights of exercise into a 'druggable' antineoplastic target(s). Given the number of 'biological' agents in many fields of medicine including oncology, cardiovascular disease and immunology, among others, there is a clear precedence

in clinical medicine. Moreover, this may provide a model to develop small molecule inhibitors/mimetic to these molecular targets. While cancer prevention is thought to be a more challenging target (given that you are treating healthy patients, the risk-benefit and cost-effective calculations become more stringent). However, the relegation of many cancers as a chronic disease underscores the clinical opportunities. Similarly, there may a combined therapeutic/preventive benefit in the increasingly important issues in cancer survivorship. Finally, there are also potential applications as biomarkers to optimize both the dosage and type of exercise (aerobic and resistance, etc.) to achieve the maximal therapeutic benefit. In this regard one could consider serum myokine(s) as a potential tool for risk stratification to allow precision medical approaches to screening strategies.

Conclusion

There is emerging evidence that myokines may have significant antineoplastic benefits and may represent a major mechanism through which the salutary benefits of exercise are transduced. This may represent a new prototype for drug discovery for both neoplastic and benign diseases. The potential for putting 'exercise-in-a-pill' may represent a major new therapeutic vista.

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