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Impact of Physical Activity In the Prevention of Colorectal Cancer

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IMPACT OF PHYSICAL ACTIVITY IN THE PREVENTION OF COLORECTAL CANCER

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DEDICATION

To my trainees: may each workout bring you closer to health and happiness.

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ABSTRACT

This review evaluates the current understanding of research on the impact of physical activity in the prevention of colorectal cancer. Current biological mechanisms implicated in physical activity and colorectal cancer risk reduction are blood glucose regulation, insulin sensitivity, leptin and adiponectin profiles, inflammation as well as secreted protein acidic and rich in cysteine (SPARC), an exercise induced myokine. Recent literature indicates that 30-60 minutes of moderate to vigorous activity a day is effective against colorectal cancer development, and there is convincing evidence of aerobic exercise as differently beneficial in recruiting mechanisms identified as preventative against colorectal cancer. This article provides a critical review of the evidence-based literature concerning the benefits of physical activity in reducing the risk for colorectal cancer. Further well designed animal and clinical trials testing differing exercise protocols are recommended for future research to enable better understanding of the currently implicated mechanisms in colorectal cancer development.

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List of Abbreviations

WHO ..... World Health Organization

AOM ..... Azoxymethane

DMH ..... 1,2-Dimethyl Hydrazine

SPARC ..... Secreted Protein Acidic and Rich in Cystine

IGF-I ..... Insulin Growth Factor 1

IGF-II ..... Insulin Growth Factor 2

IGFBP-3 ..... Insulin Growth Factor Binding Protein 3

IGFBP-6 ..... Insulin Growth Factor Binding Protein 6

DSS ..... Dextran Sodium Sulphate

IMCE ..... Immortomouse Colon Epithelial Cells

APN ..... Adiponectin

MCP-1 ..... Monocyte Chemoattractant Protein 1

BMI ..... Body Mass Index

PA ..... Physical Activity

REE ..... Resting Energy Expenditure

CHAPTER 1

INTRODUCTION

According to the American Cancer Society's 2013 statistics, colorectal cancer is the third most prevalent cancer among men and women in the United States. Despite mortality rates declining in the population over 50 years of age, rates of colorectal cancer incidence in individuals under 50 years of age are on the rise. The etiology of colorectal cancer is a complex phenomenon that involves the interaction of genetic and environmental factors. However, the vast majority of cases can be ascribed to environmental causes as they account for more than 80% of all incidences [1]. Physical inactivity has emerged as a leading environmental risk factor for colorectal cancer. According to the World Health Organization (WHO), physical inactivity is the fourth leading risk for mortality globally; it is responsible for 6% of all deaths worldwide. In fact, physical inactivity raises the risk for numerous chronic diseases such as heart disease [2-6], diabetes [7-11] and various cancers including colorectal cancer [12-17]. Physical inactivity is thought to account for 13-14% of all colorectal cancer cases [18]. Thus, the American Cancer Society speculates that the increase in colorectal cancer incidence among the younger population is, at least in part, due to a sedentary lifestyle. Conversely, physical activity or exercise training has been linked to a reduced risk for colorectal cancer; epidemiological studies indicate an inverse association between physical activity and colorectal cancer risk and controlled experiments in mice substantiate these claims. While there is an abundance of data to support a link between physical activity and

colorectal cancer risk, the mechanisms responsible for this relationship have not yet been fully elucidated.

Possible mechanisms that link physical activity to reduced colorectal cancer risk have been investigated using epidemiological studies as well as controlled experimental studies in mice. Mouse models that recreate the colorectal cancer development seen in humans have been particularly useful in examining the benefits of exercise on colorectal cancer risk in a controlled setting (i.e the dose of exercise can be controlled). For example, the $Apc^{Min/+}$ mouse that develops intestinal colon polyps similar to an aggressive case of human colorectal cancer has been widely used in exercise studies. Also, carcinogens that induce colorectal cancer including azoxymethane, (AOM) and 1,2-dimethyl hydrazine, (DMH) have been utilized to investigate the effects of exercise on colorectal cancer in both mice and rats. To date, the mechanisms that have been implicated in the benefits of physical activity on colorectal cancer risk include insulin regulation, leptin and adiponectin profiles, inflammatory processes as well as secreted protein acidic and rich in cysteine (SPARC), an exercise induced myokine. This review will examine the recent literature on the aforementioned mechanisms that are thought to link physical activity to reduced colorectal cancer risk.

CHAPTER 2

METABOLIC MEDIATORS

Metabolic mediators control growth and development, regulate energy output and storage, and work to maintain healthy body mass. Imbalances in their concentrations have been linked to a heightened risk for colorectal cancer.

2.1 INSULIN

Insulin is a hormone produced by beta cells in the pancreas; it functions to regulate blood glucose levels. Evidence indicates that insulin resistance and its associated pathological conditions including elevated fasting glucose and insulin are implicated in colorectal cancer [19]. Risk factors for colorectal cancer, including obesity, physical inactivity and type 2 diabetes are all linked to insulin resistance and hyperinsulinemia [20,21,22,23,24]. While epidemiological evidence only indirectly associates insulin with colorectal cancer risk, strong evidence implicates insulin as player in colorectal cancer. For example, insulin injections have been reported to enhance the growth of aberrant crypt foci as well as increase the number and size of colorectal tumors[2526]. Similarly, *in vivo* evidence supports a tumor promoting role of insulin on colorectal cancer cells [27,28,29,30]. Alterations in insulin may play a role in the benefits of exercise on the development of colorectal cancer. It is well recognized that exercise can decrease hyperinsulinemia. For example, in a study of one hundred Type 2 diabetic obese or overweight subjects, exercise was successful at reducing plasma insulin levels.

Within this high-risk population, a significant decrease in plasma insulin levels across all exercise modalities was reported. The greatest effect was seen in those subjects performing aerobic training in conjunction with resistance training [31]. To date, there is no direct evidence linking exercise to the prevention of colorectal cancer via a reduction in insulin levels. However, lowering baseline serum levels of insulin through exercise would presumably attenuate insulin's well-documented effects on colorectal cancer development.

2.2 INSULIN GROWTH FACTOR 1

Insulin-like growth factors (IGF-I and IGF-II) and their binding proteins (IGFBP-1 and IGFBP-6) have been linked to colorectal cancer risk in epidemiological studies as well as controlled experimental studies in mice [32,33]. IGFs promote proliferation and survival of a wide range of cell types and are thus critical for normal development. However, dysregulation of the IGF system has been implicated in a range of diseases including colorectal cancer. For example, epidemiological studies have shown that higher circulating IGF levels are associated with increased risk for colorectal cancer [34]. This relationship is supported by controlled experimental studies in mice; colorectal cancer growth is decreased in mice following deletion of the IGF1 gene [35]. *In vitro* studies have documented that the IGF-1 receptor facilitates malignant transformation of a number of oncogenes [36]. And there is an abundance of literature to support the role of IGF-1 on promotion of survival, proliferation, migration and invasion of many cell types. For example, *in vitro* IGF-1 promotes cell cycle progression and inhibition of apoptosis in several colonic adenocarcinoma cell lines [37, 29].

Exercise training has been shown to influence IGF levels, which may be a potential mechanism for the benefits of exercise on colorectal cancer. However, the dynamics of this relationship is likely heavily influenced by the intensity, mode and duration of the training regime. Several studies suggest that initiation of a training program, which is associated with a substantial increase in energy expenditure, leads initially to decreases in IGF levels. Conversely, following adaptation to the training the suppression of IGF is diminished and in fact IGF may exceed the pre-training levels. Therefore, the relationship between exercise and IGF is potentially very complex, which likely explains the inconsistent findings on its potential in the literature. For example, one study reported that voluntary wheel running exercise was associated with a lower polyp number in Apc^{min} mice but the exercise group actually showed higher IGF-1 levels; although there was no association between polyp number and IGF reported [38]. Contrary to those findings, recent literature has shown that IGF-1 levels are slightly lowered (~9%) a carcinogenic mouse model (AOM/DSS) of colorectal cancer following voluntary exercise [39]. However, the decrease was only significantly correlated with the lower colon tumor formation in AOM/DSS-treated mice when the associated increasing IGFBP-3 levels were considered [39]. Ju *et al* hypothesized a lower molar ratio of IGF-1 to IGFBP -3 (IGF binding protein) was responsible for inhibiting tumor growth in these mice [39]. Although studies in animal literature support a positive effect of exercise on IGF-1 in colorectal cancer, the evidence has been mixed, possibly due to the complex nature of IGF-1's interactions with a number of other contributing factors as well as the diversity of exercise protocols used in these studies. More research detailing IGF-1's responses to exercise are needed to formulate a better evidence base within the mouse model. To date,

there are no clinical studies on the effects of exercise on IGF-1 in colorectal cancer, this is likely due, at least in part, to the conflicting evidence foundation in the animal literature.

CHAPTER 3

ADIPOKINES

Adipose-derived hormones (adipokines), along with their customary role in energy homeostasis, have been identified as potential mediators of the effects of exercise on colorectal cancer risk.

3.1 LEPTIN

Leptin is a long-term regulator of energy expenditure and food intake. Leptin has been shown to stimulate intestinal oncogenesis through a variety of signaling pathways[40]. The hypothesized link between leptin and colorectal cancer was driven initially by reports of leptin receptor expression by various human epithelial colon cancer cell lines. When bound to leptin, the receptor can activate signal transduction pathways that can enhance cell proliferation and DNA synthesis. For example, Fenton et al., reported that leptin promotes the proliferation of preneoplastic (IMCE) cells [41]. While the *in vitro* evidence is relatively strong, there are mixed reports among the animal studies. A recent study found a significant decrease of tumor cell proliferation in leptin-deficient tumors, as well as a dramatic inhibition of tumor growth in leptin-deficient and leptin-receptor-deficient mice [42]. Whereas a previous study reported that leptin failed to promote growth of colon cancer xenografts in nude mice and did not increase intestinal tumorigenesis in $Apc^{Min/+}$ mice [43]. Clinical investigations have reported that a progressive increase in leptin occurs during colorectal carcinogenesis [44]. Taken together, the available literature suggests that lowering baseline levels of leptin could lower risk for developing colorectal cancer. It

has been shown that exercise can significantly reduce baseline leptin levels in APC ^{Min} mice [45]. However, it is important to note that while small changes were seen in male polyp development, no decrease in female mice tumor load was observed; therefore, the relevance of these findings are inconclusive. Follow up studies by Colbert *et al* demonstrated that a greater frequency and duration of voluntary wheel running decreased male polyp count by 25%, but in those studies, energy balance, rather than leptin was the mechanism investigated [38]. Citing Colbert et al's decision to conclude investigating leptin mechanistically after their first study, it can be presumed that although dated animal research found that exercise was effective in lowering baseline leptin levels, current research does not support a leptin mediated link between exercise and colorectal cancer prevention. However, it is important to note that the observed decrease in leptin with exercise, independent of colorectal cancer, is likely due to the exercise-induced decrease in fat mass.

3.2 ADIPONECTIN

Adiponectin (APN) is an adipokine secreted exclusively by adipose tissue, which has been reported to be negatively associated with colorectal cancer risk; a decrease in adiponectin is associated with increased risk for colorectal cancer. Adiponectin's suppressive role in tumorigenesis has been widely documented in mouse models of colorectal cancer [46,47]. More recent animal studies have used APN deficiency models to mechanistically determine its role in both the risk and development of colorectal cancer. For example, Saxena *et al* reported that APN deficiency was associated with higher expressions of pro-inflammatory and pro-cancerous markers [48]. Further, APN knockout mice showed greater tumor numbers as well as greater tumor area due to an increase in

colonic mucosal erosion that resulted from a thinning of the mucosal lining [49]. Another study examined the role of APN in a carcinogenic as well as a genetic mouse model of colorectal cancer. It was found that deficiency of APN increased tumorigenesis in both models; in the $Apc^{min/+}$ mouse model APN-/- increased tumorigenesis by 3.2 fold and in the carcinogenic model by ~70% [50].

Several studies have examined the benefits of exercise on APN in the settings of colorectal cancer. To date, Saxena *et al* has reported the most promising data to support the protective effects of exercise on colorectal cancer development. They report increased serum levels of APN by exercise training and suggest that it may be one of the mechanisms for the protective role of exercise of inflammatory processes in a carcinogenic mouse model of colitis. [51]. As expected, their APN deficient mice were more susceptible to inflammation than their wild-type counterparts and the benefits of exercise on inflammation were lost in their APN deficient mice. Other studies have demonstrated similar effects of exercise on APN levels. Tang *et al* noted a particularly interesting shift of APN levels in rats in response to exercise. High fat diet feedings for 8 weeks decreased circulating APN levels; however, 8 weeks of exercise training reversed this effect [52]. Such results prove promising for prompting additional studies to improve our understanding of the effects of exercise on adiponectin in the settings of colorectal cancer.

As with the animal literature, higher levels of APN have been implicated in having a protective role in the development of human colorectal cancer. For example, an inverse relationship between serum APN and colorectal cancer grade was observed in a recent case study involving subjects diagnosed with colorectal cancer [53]. Further, the

benefits of exercise on APN have also been investigated, although not in the settings of colorectal cancer. To date, few clinical trials have investigated the specific effects of exercise on APN levels. This is presumably due to the fact that the effect of exercise on circulating APN levels varies by individual; this may be attributed to variances in genes or environmental factors [54]. A study by Lee *et al* sought to understand the activity of APN polymorphisms and completed a study on obese women having variations of two polymorphisms of the APN gene that are reported to be associated with insulin resistance and APN levels [55]. They found that regardless of polymorphism, aerobic training over 3 months increased circulating APN levels [56]. Because studies in mouse models have reported that an increase in APN levels decreases polyp development and load, presumably these subjects would have attenuated risk for colorectal cancer given the exercise-induced increase in APN. In addition, these individuals had a significant decrease in body weight, BMI, and waist circumference, which would also mitigate their risk of developing colorectal cancer. Although the clinical literature available seems promising, further clinical studies are needed to confirm the link between exercise, adiponectin and the development of colorectal cancer outside the animal model.

CHAPTER 4

INFLAMMATION

The colon has evolutionarily outfit itself with a large population of immunologically active cells to defend the body against invasion and to regulate homeostasis [57]. It is through their modulation that the release of inflammatory cytokines is regulated [58]. If, over time, these cells are constantly expressing higher than normal levels of these inflammatory cytokines it can lead to chronic intestinal inflammation. It has been hypothesized not only that colorectal cancer pathogenesis may be influenced by the state of this chronic intestinal inflammation [59], but also that regular exercise is capable of mitigating it.

4.1 TNF ALPHA

TNF-α is a cytokine involved primarily with systemic inflammation. Its effector cells (immune cells) regulate the inflammatory response to a number of different assaults and through initiation of a variety of inflammatory cascades. TNF-α has been found to be a main stimulant of colitis-associated colorectal cancer [59]. The most likely mechanism for this response is that TNF-α elevates the activity of inflammation-sensitive transcription factors such as NF-κB [60] as well as the inflammatory cytokines IL-6 and IL-1β [61]. We have shown that TNF-α mRNA expression is increased in the intestines of the $Apc^{Min/+}$ mouse, which is associated with the abundance of large polyps [62]. Further, using a monocyte chemoattractant protein 1 (MCP-1) knockout mouse we have reported a decrease in the number of macrophages in the polyp tissue, which was linked to a

reduction in TNF-α expression [63]. This is of particular importance given that the predominant expression of TNF-α in colorectal cancer is observed within tumor associated macrophages [64]. Direct evidence for the involvement of TNF-α in cancer comes from observations that antibodies against TNF-α inhibit the development of inflammation-related colon cancer [65].

While the available literature on the benefits of exercise on TNF-α in colon cancer is limited, the studies that are presented are promising. For example, recently it has been shown that regular exercise suppressed the generation of aberrant crypt foci in the colon following AOM and this was associated with decreased levels of TNF-α in both the colon and plasma [66]. Similarly, TNF-α expression in intestinal lymphocytes of younger C57BL/6 mice has been shown to be decreased with voluntary wheel running exercise suggesting that long term exercise may protect the bowl by reducing intestinal inflammation [67]. Further, a recent study in aged C57BL/6 mice demonstrated that regular exercise lowered TNF-α in plasma and serum [68]. Although good evidence for a benefit of exercise on TNF-α in colorectal cancer in animals is beginning to accumulate in the literature, the clinical data is disappointingly sparse and relatively undocumented. None-the-less a team in India has demonstrated that humans respond accordingly to regular exercise, with over 70% of subjects lowering their baseline values of TNF-alpha after one month of moderate exercise [69].

4.2 IL 6

Interleukin-6 or (IL)-6 is a pleiotropic cytokine that modulates a variety of physiological responses and activates genes associated with cellular proliferation, differentiation, and apoptosis. Epidemiological studies indicate an association between

IL-6 and colorectal cancer and controlled experiments in mice substantiate these claims. This effect is thought to be largely mediated through its ability to increase intestinal inflammation [70]. A recent study reported that IL-6 expression in stage III colon cancer patients is a prognostic marker of tumor behavior [71]. Further, using IL-6 knockout mice as well as IL-6 overexpression techniques, Baltgalvis *et al*., eloquently examined the role of IL-6 on tumor characteristics in the $Apc^{Min/+}$ mouse model of colon cancer. They reported that knocking out IL-6 reduced the number of large polyps by approximately 30% and these effects were reversed when IL-6 was overexpressed [72]. Interestingly, they also demonstrate that IL-6 is necessary for the onset of adipose and skeletal muscle wasting in the $Apc^{Min/+}$ mouse as IL-$6^{-/-}$ mice did not lose gastrocnemius muscle mass or epididymal fat pad mass while IL-6 overexpression led to a decrease in mass for each of these tissues.

IL-6 has been implicated in the link between exercise and colorectal cancer; several studies have reported a benefit of exercise on IL-6 in colorectal cancer. One study reported that nine weeks of moderate treadmill running decreased total intestinal polyps by 29% in male $Apc^{Min/+}$ mouse and this was associated with a 98% decrease in IL-6 [73]. A follow up study by the same group documented that moderate-intensity treadmill exercise can attenuate IL-6-dependent cachexia in $Apc^{Min/+}$ mice, independent of changes in IL-6 concentration and muscle inflammatory signaling [74]. The exercise effect was associated with improved insulin sensitivity and improved energy status in the muscle. Similarly, IL-6 induced mitochondrial remodeling and proteolysis was documented to be rescued with moderate exercise training even in the presence of high circulating IL-6 levels [75]. While there is good evidence to support an effect of exercise

on IL-6 in mouse models of colorectal cancer, there is very little clinical evidence in this area. Although given the well documented effects of moderate exercise training on reducing IL-6, it is likely that these same outcomes will be seen in the human literature.

CHAPTER 5

SPARC

It has been postulated that the exercise-induced production of novel myokines can alter the mechanisms involved in colorectal cancer pathogenesis. In a recent study, Aoi *et al.* suggested that the anti-tumor effect of regular exercise was more dependent on circulating factors rather than endogenous proteins in the colon [66]. One such myokine, secreted protein acidic and rich in cysteine (SPARC) also known as osteonectin, is a matricellular protein that is involved in cell to cell interaction, growth factor function and cell differentiation [76]. A recent study by Aoi *et al* examined the effects of exercise on the expression of this novel myokine in the muscle of mice and humans following a single bout of exercise. It was found that a single bout of aerobic exercise increased plasma levels of SPARC in both humans and mice via promotion of SPARC upregulation in contracting myocytes [77]. Although SPARC returned to baseline levels after 6 hours in humans, their studies demonstrate that regular exercise enhanced the secretory ability of SPARC in response to muscle contraction by increasing the amount of SPARC in resting muscle tissue [77]. Using SPARC knockout mice, they went on to examine if the benefits of exercise on colorectal cancer may be mediated by SPARC. They found that low-intensity exercise reduced aberrant crypt foci growth in a chemically-induced mouse model of colorectal cancer. However, the benefits of exercise were lost in SPARC deficient mice implicating a role of SPARC on the benefits of exercise in colorectal cancer. Further, exercise enhanced apoptosis in colon mucosal cells but again these

effects were not evident in SPARC deficient mice. These recent findings concerning up-regulation of SPARC via aerobic exercise provide yet another outlet to investigate the promising effects of exercise in prevention of colorectal cancer. Further studies are needed to better elucidate SPARC's effects on the known mechanisms of colorectal pathogenesis.

CHAPTER 6

PHYSICAL ACTIVITY AND EXERCISE RECOMMENDATIONS

Physical activity (PA) is defined by the American College of Sports Medicine as any bodily movement created from muscle contraction and resulting in an energy expenditure increase over that of resting energy expenditure (REE). Exercise is a planned and structured form of PA that uses repetitive bodily movement to improve or maintain one or more components of physical fitness, which are simply characteristics that allow one to perform physical activities.

The World Health Organization's Global Recommendations on Physical Activity for Health (2008) focus mainly on type, duration, frequency, intensity, and volume of physical activity. These recommendations are minimum guidelines allotted to provide benefits in cardiorespiratory health, metabolic health, bone health, depression and breast and colon cancer. WHO recommends at least 150 minutes of moderate intensity aerobic physical activity or at least 75 minutes of vigorous physical activity per week. WHO's guidelines also note that at least 30-60 minutes per day of moderate to vigorous activity is needed to observe significantly lower risks of breast and colon cancer [78].

While epidemiological data suggested higher durations of physical activity is protective against colorectal cancer, the early animal literature was inconclusive. Colbert *et* al noted that while prior epidemiological studies and studies in chemically induced cancerous rats concluded a beneficial influence of exercise on tumor polyp load, their 2002 work provided limited evidence for possible preventative effects against intestinal

tumorigenesis in male *Apc*$^{min/+}$ mice, and no evidence for an effect in female *Apc*$^{min/+}$ mice [45]. Subsequently, advances in exercise protocols as well as additional investigation into pivotal mechanisms surrounding the development of colorectal cancer have established a dose-response relationship supporting the suppressive nature of exercise on colorectal cancer.

Recent studies by Colbert *et al* with C57BL/6J-Apc^{Min} mice reported that voluntary treadmill running and the negative energy balance resulting from pair-feeding with a non-exercising control group decreased polyp number in a dose dependent manner in the running group. The running group also maintained a significantly smaller overall body weight than the control group [38]. Similarly, another study reported that forced low-intensity running and forced swimming reduced aberrant crypt foci, precursors to colonic adenocarcinomas, sustained from carcinogenic DMH-injections in rats [79,80]. More recently, in mice subjected to azoxymethane (AOM) injections, a tri-weekly running schedule for six weeks decreased aberrant crypt foci development compared to a sedentary treatment [66].

While there is ample evidence to support a lower incidence of colorectal cancer development in animal models with higher levels of aerobic exercise, the clinical data supporting such a link is scarce by comparison. However, McTiernan *et al*, found a 12-month exercise intervention of 60 minutes per day 6 days a week decreased colonic crypt cell proliferation in healthy human subjects [81]. Because an increased cell proliferation rate and an extension of the normal proliferative zone within the colon crypt are reversible precursors of colonic neoplasia [82], these subjects, having lowered their proliferation rates, would have attenuated their risk for developing colorectal cancer.

Likewise, a 2011 meta-analysis of 20 clinical studies of physical activity and colonic polyps by Wolin *et al* concluded a significant inverse relation between physical activity and colon adenomas or polyps. Wolin *et al* conclude that physical activity may reduce the risk of colon polyp development by 15%. The reduction of risk by physical activity may also be substantially greater for large and advanced polyps [83]. Recent cohort studies also mirror animal and clinical findings on the positive role of physical activity on colon cancer risk. A 2012 screening study of 912 multi-ethnic persons scheduled for an exam concluded that more than 60 minutes of exercise a week, was correlated with a low or no polyp count. Subjects who performed at least 60 minutes of exercise weekly were less likely to have any detectable polyps compared to those who did not regularly exercise. They were also less likely to have an adenoma on their colonoscopy compared to their counterparts with more sedentary lifestyles [84]. The questions in the study pertaining to exercise were asked in a manner that inferred activity outside daily activity, i.e. exercise. Unfortunately, mode of exercise was not investigated in this study.

CHAPTER 7

CONCLUSION

The current body of evidence supports a positive effect of exercise, and in particular vigorous aerobic activity, on the prevention of colorectal cancer. Animal studies support the hypothesis that exercise mediates this protective effect by inducing changes in blood glucose regulation, insulin sensitivity, the adiponectin profile, inflammation regulation and SPARC secretion. For a better understanding of these mechanisms and their role in preventing tumorigenesis, further studies containing even more exercise protocol variations should be completed. Granted the scarcity of current clinical data, future clinical studies are needed to support the conclusions of these animal studies. Further advancements within this field are important for public health prevention practices and awareness that may aid in nudging the population towards healthier lifestyle choices.

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