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Review

Cancer Prevention Research

PGC-1α as a Biomarker of Physical Activity-Protective Effect on Colorectal Cancer

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Abstract

Colorectal cancer is a significant public health concern. As a multistage and multifactorial disease, environmental and genetic factors interact at each stage of the process, and an individual's lifestyle also plays a relevant role. We set out to review the scientific evidence to study the need to investigate the role of the *peroxisome proliferator–activated receptor gamma coactivator 1 alpha (PGC-1α)* gene as a biomarker of the physical activity's (PA) effect on colorectal cancer. PA is a protective factor against colorectal cancer and usually increases the expression of *PGC-1α*. This gene has pleiotropic roles and is the main regulator of mitochondrial functions. The development of colorectal cancer has been associated with mitochondrial dysfunction; in addition, alterations in this organelle are associated with colorectal cancer risk factors, such as obesity, decreased muscle mass, and the aging process. These are affected by PA acting, among other aspects, on insulin sensitivity and oxygen reactive species/redox balance. Therefore, this gene demands special attention in the understanding of its operation in the consensual protective effect of PA in colorectal cancer. A significant amount of indirect evidence points to PGC-1α as a potential biomarker in the PA-protective effect on colorectal cancer. The article focuses on the possible involvement of *PGC-1α* in the protective role that physical activity has on colorectal cancer. This is an important topic both in relation to advances in prevention of the development of this widespread disease and in its therapeutic treatment. We hope to generate an initial hypothesis for future studies associated with physical activity–related mechanisms that may be involved in the development or prevention of colorectal cancer. *PGC-1α* is highlighted because it is the main regulator of mitochondrial functions. This organelle, on one hand, is positively stimulated by physical activity; on the other hand, its dysfunction or reduction increases the probability of developing colorectal cancer. Therefore, we consider the compilation of existing information about the possible ways to understand the mechanisms of this gene to be highly relevant. This study is based on evidence of PGC-1α and physical activity, on PGC-1α and colorectal cancer, on colorectal cancer and physical activity/inactivity, and the absence of studies that have sought to relate all of these variables.
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Introduction

Colorectal cancer is a multistage and multifactorial disease. Different environmental and genetic factors interact at each stage of the process (1); the individual's lifestyle also plays a significant role (1). From a public health point of view, it needs attention, as it is estimated that about 1.5 million new cases and 700,000 deaths occur every year (2), and it is more prominent in the more developed countries. Its incidence is increasing in many countries, especially those in economic transition (3). It has a higher incidence in people older than 50 years. It is also observed to be more frequent in men, whose mutations have been related to the environment, especially to lifestyle, with a higher incidence of sporadic cases (1). Physical inactivity is a significant risk factor for presenting with colorectal cancer (4). In fact, it is thought to increase the chances of developing colorectal

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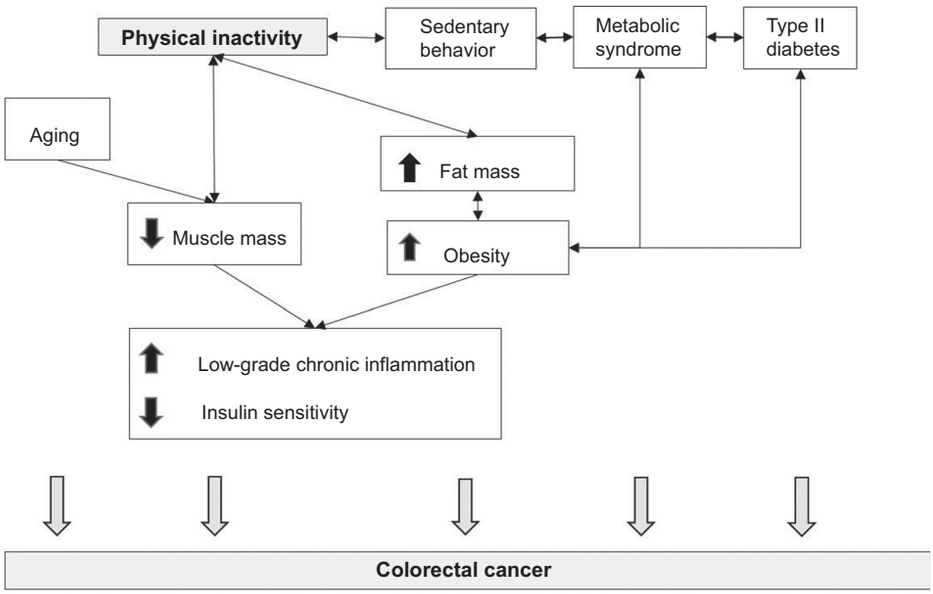

Figure 1.
Physical inactivity and risk factors of colorectal cancer. Physical inactivity impacts health in a negative way, encouraging sedentary behavior as well as an increase of the fat mass and a decrease of muscle mass with their respective consequences. In addition, the aging process reinforces those negative aspects, largely with alterations in muscle mass. The aging process, physical inactivity, sedentary behavior, obesity, metabolic syndrome, and diabetes type II are all risk factors of colorectal cancer, and they are all interconnected in some way.

cancer by 33% and has been suggested to be a causal factor in 10% of cases (5). It has been estimated that approximately 43% of people with colorectal cancer have a very low level of physical activity (PA; ref. 5), which could lead to an increased risk of mortality (6).

The fact that physical inactivity has been related to the probability of developing colorectal cancer is supported by a whole series of risk factors for the disease, such as overweight and obesity, type II diabetes, and metabolic syndrome (7, 8), which are a result of sedentary behavior. Recently, it has also been determined that loss of muscle mass may be a factor of incidence in colorectal cancer (ref. 9; Fig. 1).

PA is considered a protective factor against colorectal cancer (10) not only because it contributes to combating the risk factors previously mentioned but also because it acts on other precancerous forms, such as adenomas and polyps in the colon (11).

Although the relationship between PA and colorectal cancer is well established, the mechanisms that support it still need attention (12). It is thought to be relevant to mechanisms related to insulin sensitivity, adiposity, and inflammatory processes (13, 14). These factors have several characteristics in common, highlighting the fact that they are all related to mitochondrial functions (15, 16). Considering that mitochondrial dysfunction is involved in cancer (17, 18) and that the *peroxisome proliferator–activated receptor gamma coactivator 1 alpha (PGC-1α)* is a mitochondrial regulator (19), which one can observe in a wide variety of biological processes—such as thermogenesis, circadian rhythm, fatty acid oxidation, glucose metabolism, mitochondrial organization, and biogenesis—it responds to reactive oxygen species (ROS) or conformation of muscle fiber types (20, 21). Taking into account that its expression is altered by energy demand, *PGC-1α* is related to a whole series of risk factors linked to physical (in) activity. Thus, it is important to study the relationship between colorectal cancer, physical (in)activity, and *PGC-1α*. This article reviews the scientific evidence to justify the need to investigate the role of *PGC-1α* as a biomarker in colorectal cancer prevention.

The role of PGC-1α

Among the great variety of biological processes in which *PGC-1α* is involved, it is the main regulator of mitochondrial biogenesis (MB), oxidative metabolism, and antioxidant defenses (22, 23). PGC-1α performs its functions by interacting with transcription factors of both nuclear [i.e., PPARγ and estrogen-related receptor (ERRα)] and nonnuclear (i.e., cAMP response element binding and Forkhead Box protein O1) receptors through the modulation of their target genes, which are implicated in various metabolic pathways, such as gluconeogenesis, fatty acid synthesis or oxidation, or glycolysis (23, 24). Specifically, regarding MB, PGC-1α coactivates nuclear respiratory factors 1 and 2, which are regulators of mitochondrial transcription factor (TFAM) expression. TFAM is a recognized nuclear encoding factor that develops functions essential for the replication, maintenance, and transcription of mitochondrial deoxyribonucleic acid (25).

The activity developed by PGC-1α in the tissues is extremely varied, because it does not present common target genes in each tissue (26). Thus, its expression is the reflection of the cellular energy demands in different tissues (24). As a consequence, *PGC-1α* presents greater expression in tissues with high energy demand such as the heart, skeletal muscle, liver, central nervous system, and fatty tissue (21, 27, 28). It has minor, but not less important, expression in other tissues, such as the intestinal epithelium (29).

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The regulation of *PGC-1α* occurs in different ways, depending on the target organ in which its activity takes place (21, 30). Thus, in the skeletal muscle, PGC-1α is phosphorylated by both p38MAPK and AMP-activated protein kinase (AMPK), allowing greater molecular stability and activation of that protein (24, 27). In the liver, the regulation of PGC-1α occurs via the insulin signaling pathway (Akt/protein kinase B), producing the opposite result via its phosphorylation (reduction of stability and decrease in its activity; ref. 27). In brown adipose tissue, PGC-1α interacts with PPARγ, activating the promoter of the gene coding for uncoupling protein 1 (UCP1), whereas in adipocytes, it activates the adipocyte lipid–binding protein gene, a well-known PPARγ target (31). Several triggers for its activation, both environmental (i.e., low temperatures) and lifestyle related (i.e., nutrient restriction or physical exercise), have been identified (24).

Colorectal cancer and PGC-1α

As a carcinoma, colorectal cancer is triggered by an imbalance between proliferation and programmed cell death (32), which are both dependent on adequate regulation of energy metabolism (33). This dependence results in the relationship among some of the mechanisms proposed for the association of mitochondrial dysfunction and cancer, such as high production of ROS, alterations in glucose metabolism, and alterations in apoptotic function (34). All of these factors are related to the reported *PGC-1α* functions and suggest a relationship between this gene and colorectal cancer, as described previously (ref. 35; Fig. 2).

The increase in ROS concentration is considered to be of vital importance in the development of colorectal cancer, because it can lead to genomic instability, which translates into an imbalance between the development of mutations and the mechanisms of control of the cell cycle (36). Genomic instability is present in the development of colorectal cancer (37), either through chromosomal instability or microsatellite instability (37), associated with crypt cells and intestinal surface (29). Considering that *PGC-1α* is poorly expressed at the bottom of the crypt and highly expressed in the upper part of the villi, where the highest concentration of ROS exists, it suggests that a relationship exists between this gene and the main pathways that allows the development of colorectal cancer. However, this relationship is not fully understood. On one hand, PGC-1α is the regulator of oxidative phosphorylation by activation of the nuclear respiratory factors previously discussed, and the respiratory chain is the point of greatest cellular production of ROS (22). On the other hand, PGC-1α is an important regulator of antioxidant defenses, promoting cellular homeostasis. However, it has been suggested that the high accumulation of ROS in the intestinal epithelial surface is owing to an imbalance between the increase in mitochondrial respiration and the reduced activity of the antioxidant enzymes, thus being protective against colorectal cancer, which would affect the increase of apoptosis and cell renewal (38).

Corroborating this finding, Feilchenfeldt and colleagues (39), after analyzing dysplastic and normal mucosal samples in patients with colorectal cancer, found that the former had a reduction in the expression of *PGC-1α* of around 60%. As we can see, D'Errico and colleagues (29) observed a reduction of 70% and 90% in the *PGC-1α* mRNA in dysplastic intestinal mucosa of rats. However, conflicting findings have been reported. Thus, Bhalla and colleagues (40), comparing the overexpression and low expression of *PGC-1α* in rats, observed that the decrease in PGC-1α levels also reduced the formation of intestinal polyps, which could indicate a promoter role in colorectal cancer. In addition, when colorectal cancer is established, it has been reported that PGC-1α may contribute to cell survival, whereas it acts against large amounts of ROS generated by chemotherapy treatments (41). These differences could be due to several mechanisms still being investigated: (i) PGC-1α acts on both catabolic and anabolic functions (33); (ii) the coordination between the

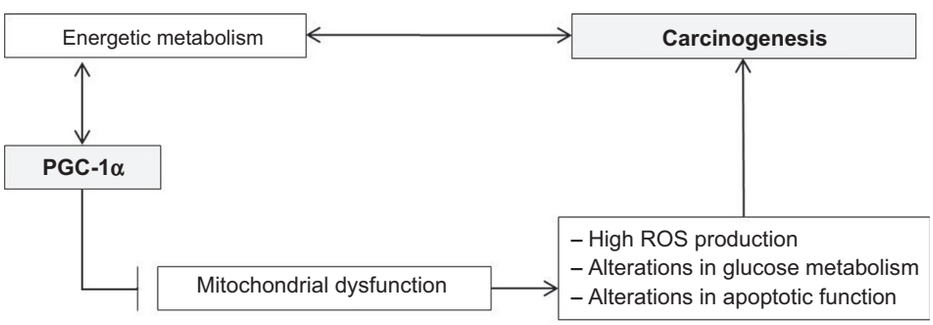

Figure 2.

Mitochondrial dysfunction and carcinogenesis. Mitochondrial dysfunction is related to a high ROS production, glucose metabolism alterations, and alterations in apoptotic function. These are factors that increase carcinogenesis. Carcinogenesis alters the energy metabolism. Energy metabolism is linked with mitochondrial function that is regulated mainly by PGC-1α. When this gene is in the normal condition, it decreases the probability of mitochondrial dysfunction. This could help to decrease carcinogenesis.

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proteins encoded in the nucleus and in the mitochondria is altered (42); (iii) methodologic differences are employed in the studies (43), mainly those related to the stages of development of colorectal cancer (44); and (iv) heterogeneity in *PGC-1α* expression among tumor subpopulations (45).

Furthermore, it could be in agreement with the Warburg effect, in which tumor cells primarily use glycolysis for ATP generation (46), and then, with cancer progression, in addition to glycolysis, via the oxidative pathway is increased to maintain the necessary energy input required for the proliferation of cancer cells (16), with an exacerbated increase in the number of mitochondria (19).

Recent findings indicate that mitochondrial dysfunction, rather than having a causal effect on cancer, may be the consequence of the mitochondrial reprogramming that it requires (47). In this line of reasoning, Jones and colleagues (32) make clear the importance of MB for cellular processes or for the maintenance of functional mitochondria capable of meeting energy demands or as an adaptive mechanism in response to the variation of energy requirements. In addition, they emphasize the importance of the PGC family not only in functions related directly to the mitochondria but also in those indirect functions concerning cellular metabolic activity, emphasizing that the dysfunction in the PGC family can be the basis of pathologies such as cancer. This finding is reinforced by the works of Luo and colleagues (45) and Alonso-Molero and colleagues (48), which also highlight the importance of identification of various pathways regulated by the PGC-1 family as well as the different components that are influenced and affected by it.

PGC-1α and PA

PA, understood as any voluntary movement that generates energy expenditure, has a significant impact on body tissues, specifically on skeletal muscle, which is both the generator of movement and an endocrine organ (49). Muscle under insulin-stimulated conditions can remove 70% to 90% of a glucose load (23) and has a high plasticity capacity (50). Energy status is central to body systems' functioning and the physiologic responses derived from muscle actions, and promotes MB (51). *PGC-1α* is the major regulator of MB; its activation and expression is enhanced by both the AMPK pathway and p38MAPK, as well as by response to calcium-dependent nerve stimulation by activation of calcium/calmodulin-dependent protein kinase (CaMK) and calcineurin A (52, 23). These pathways respond to an increase in AMP and diphosphate and ROS or calcium, respectively, which, in turn, are increased by different types of muscle contractions (53, 54). When endurance is prioritized, PGC-1α promotes phenotypic adaptations in skeletal muscle toward a more oxidative phenotype (23, 50), and, in response to acute-altered energy demands, PGC-1α relocalizes into nuclear and mitochondrial compartments, where it works as a transcriptional coactivator for both nuclear and mitochondrial DNA transcription factors promoting MB (55). Increased *PGC-1α* expression results in improved mitochondrial respiratory function, enzymatic activity, and mitochondrial content (43). There are other physiologic responses derived from PA in which a fundamental role of PGC-1α is indicated, such as increased angiogenesis, a regulation pattern of substrate selection, and an anti-inflammatory effect (27, 56, 57). This assumption is based on the fact that *PGC-1α* is a promoter of angiogenesis by *VEGF* (58) and aids in the uptake of glucose by increased expression of *glucose transporter isoform 4 (GLUT4*; refs. 59, 60), which is involved in the metabolism of acids, fatty acid by *PPAR*(28), and reduced phosphorylation of *p65* (member of the NFκB family; ref. 57). MB and fatty acid oxidation induced by PGC-1α allows integrated upregulation in fatty acid oxidation with improvements in insulin sensitivity (23). Note also that *PGC-1α* appears to be involved in preserving the integrity of the neuromuscular junction [ref. 61; a factor that, when altered, may promote sarcopenia (62)] and its expression is related to preservation of muscle mass, decreasing proteolysis (63).

Scientific evidence indicates that *PGC-1α* is also related to physical deconditioning processes that accompany an inactive lifestyle. For example, in rats, it was verified that the absence of PA results in the loss of muscle oxidative phenotype (mitochondrial fragmentation, loss of mitochondria, reduction of mitochondrial oxygen consumption, and decreased expression of mitochondrial respiratory chain genes), which is accompanied by a decrease in levels of *PGC-1α* (64). As a consequence, this decrease is more pronounced in muscles with a greater oxidative component (65). The absence of this gene reduces the muscular mitochondrial content, as has been verified in laboratory animals with a *PGC-1α* knockout model (66). This physiologic response may induce muscular atrophy as a consequence of the existence of fibrillary damages and an increase in inflammatory markers along with worsening glucose tolerance, thus affecting the capacity to engage in PA (65, 67).

It should be noted that muscular deconditioning is frequently observed in people with colorectal cancer, which could be palliated thanks to the protective role that PGC-1α plays on protein catabolism and muscle homeostasis (63). Actually, Zampieri and colleagues (68) found a surprisingly high percentage of myofibers with internalized or central nuclei in patients at clinical onset of colorectal cancer with a higher percentage of fast-twitch fibers compared with slow type.

Finally, engaging in exercise is a stimulus that leads to an increase in the activation and expression of *PGC-1α*, which has consequences beyond muscle tissue. It has been suggested that PGC-1α may act on other tissues through myokines such as irisin, stimulated by PGC-1α by

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expressing various muscle genes, such as *fibronectin type III domain containing protein 5* (69, 70). This myokine has been described as a promoter of *UCP1* expression, which, in turn, significantly increases total body energy expenditure and reduces obesity-related insulin resistance (71). Perhaps this is one of the reasons that in transgenic rats, the increase in muscle PGC-1α concentration generated resistance to the development of obesity related to age and diabetes and an increase in life expectancy (72).

In addition, it is probable that people who do not engage in PA may become overweight or even obese in relation to people who do exercise. It is important to understand that, in adipose tissue, expression of *PGC-1α* seems to be lower in morbidly obese than in slim subjects (73). Moreover, this low expression could be correlated with low expression of genes such as *UCP-1* in this tissue, supporting previous observations and suggesting that the differential expression of *PGC-1α* may be involved in the regulation of adipose tissue and skeletal muscle, as has been proposed by Hammarstedt and colleagues (74).

Another important factor is the contribution of PGC-1α in decreasing inflammatory markers, linking metabolic and immune pathways (57). In this sense, the association of colorectal cancer with chronic inflammatory processes is known, although these processes may have a double function: they may act to promote the eradication of the growing tumor cells or they may help the development of the tumor, making it difficult for the immune system to recognize tumor cells, thus creating a proper medium for their progression (75). In addition, Olesen and colleagues (76), based on a study with rats, suggest that lower levels of PGC-1α in the muscle decrease the effectiveness of the body's responses to infections.

According to Kruk and Czerniak (77), PA can impact all stages of carcinogenesis through different mechanisms, such as decreased adiposity, decreased insulin resistance, improved immune function, and reduced inflammation—processes that, according to the studies mentioned here, are associated with *PGC-1α*. In fact, PA increases *PGC-1α* expression in all adipose tissue types. It results in increased expression of genes involved in MB, increased mitochondrial activity, increased beiging of subcutaneous white adipose tissue (WAT), and an altered adipokine profile (78). However, the mechanisms are different among each type of adipose tissue and are also still to be determined. The most described mechanism is in brown adipose tissue, which is a potential therapeutic strategy for weight loss in obesity, and is related to heat production (79). Accumulation of visceral WAT is associated with insulin resistance and an increased risk of type II diabetes. This is in contrast with what is observed in subcutaneous WAT (78). Compared with visceral WAT, subcutaneous WAT has a higher expression of many genes involved in glucose homeostasis and insulin action, such as *PPARγ*, coactivated by *PGC-1α*. Furthermore, genes involved in Wnt signaling (colorectal cancer via) and PGC-1α–related pathways were significantly increased in subcutaneous WAT with physical exercise (78).

Therefore, an increase in gene expression appears to be an important response of the adaptive process to PA, which, to a large extent, is related to the mechanisms or factors present in the development of colorectal cancer.

PA and colorectal cancer

Current scientific evidence indicates that inactive individuals are at increased risk for colorectal cancer (4, 10). Thus, for example, Moore and colleagues (80) observed that both moderate and vigorous recreational PA is a protective factor both for colon cancer and for rectal cancer [HR, 0.84; 95% confidence interval (CI), 0.77–0.91 and HR, 0.87; 95% CI, 0.80–0.95, respectively]. Simons and colleagues (81) found that occupational activities with higher levels of energy expenditure (>12 kJ/minute vs. <8 kJ/minute) and shorter sitting times (<2 vs. 6–8 h/d) were associated with a lower propensity to develop colon cancer. Similarly, Kyu and colleagues (82) observed that people who accumulated more than the 600 MET min/wk of PA recommended by the World Health Organization, independently of the domain to which it refers, presented a lower risk of developing this type of cancer (82).

However, there is still scant scientific evidence regarding the impact of the factors related to PA (type, volume, intensity), how it is performed, the individual histories of participants (PA experience), and its cost–benefit ratio in relation to colorectal cancer (83). In this sense, over the past few years, increasing scientific research has been conducted regarding the effects of different physical activities on colorectal cancer. Nevertheless, the vast majority is focused on the effects of PA on survivors of this type of cancer without clear evidence of how to proceed (84). Moreover, in survivors, the mechanisms that justify the benefits of PA in colorectal cancer patients are uncertain. Insulin alterations, visceral adipose tissue, adiponectin, TNFα levels, and fatigue have been proposed (85, 86). Regarding prevention, an interesting study was carried out by Campbell and colleagues (87), who, through a randomized intervention based on aerobic exercise (6 d/wk for 12 months, with an intensity of 60% to 85% of maximal heart rate) with a group of sedentary adults, observed an increase in the apoptotic potential of the crypt only in men who participated in training versus controls (those who followed their normal routines). This result could be in line with the maintenance of the balance between cell proliferation and apoptosis to avoid the development of neoplastic tissue, largely responsible for the Bcl-2 and Bax proteins in the colon. Bax protein, a promoter of apoptosis through mitochondrial membrane permeabilization (88), was identified as a fundamental molecule for the performance of *PGC-1α* in the intestine

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(38), and it could be an important link between PA and its protective effect in colorectal cancer through that gene. However, in the study by Campbell and colleagues (87), this result was not observed in women, which highlights what was suggested by epidemiologic studies describing that PA has a greater protective effect against colorectal cancer in men.

Regarding the influence that PA might have on the expression of *PGC-1α*, it seems that the intensity of PA is one of the main factors to take into account. Thus, in healthy young men, it has been observed that after 4 weeks of training with different matched for total work protocols, those who participated in the more intense protocol (200% of peak power output) obtained greater expressions of the gene when compared with the protocols performed at 90% and 65% of peak power output (89). Similarly, in a study carried out with a comparable sample that analyzed the effect of just one exercise session on the expression of *PGC-1α*, they verified that at higher intensities, the highest increase of the mRNA of *PGC-1α* is manifested 3 hours after cessation of the stimulus (90). A similar result was observed by Gibala and colleagues (91) following an acute protocol of four sets of 30 seconds all-out with a 4-minute interval between them. The results of these studies invite us to consider that exercise intensity modifies *PGC-1α* expression levels.

PGC-1α, PA, and colorectal cancer

In the absence of investigations that simultaneously relate PA, *PGC-1α*, and colorectal cancer prevention at the molecular level, and taking into account the previous discussion, we considered some possible factors in common among these three variables, highlighting the following risk factors of colorectal cancer: obesity, decreased muscle mass, and the aging process (Fig. 3). We highlight these risk factors because they respond positively to the performance of PA and because they share two common points: they affect insulin sensitivity and alter the ROS/redox cellular balance with their respective consequences.

In muscle, *PGC-1α* expression levels, in addition to responding to the pathways discussed (AMPK, CaMK, p38MAPK), also appear to be regulated by the insulin signaling pathway with complex regulatory mechanisms that are not yet completely clear. Although some studies report that insulin increases the transcription of *PGC-1α*, others theorize that it may have the opposite effect, as insulin media stores energy and decreases catabolic pathways (24).

According to Keku and colleagues (92), it has been observed that the lack of insulin sensitivity causes an increase in insulin concentration. This promotes the appearance of colorectal adenomas by decreasing the cellular apoptosis of the normal intestinal mucosa (92). Thus, it seems essential to understand that physical exercise, as a stressor that demands energy, stimulates *PGC-1α* expression, increasing both MB and glucose uptake (increase of GLUT4; 93). In response to this increase and to the respective mitochondrial functions, we observed an improvement in insulin sensitivity (94), which can lead to a decrease in the risk of colorectal cancer. Therefore, the

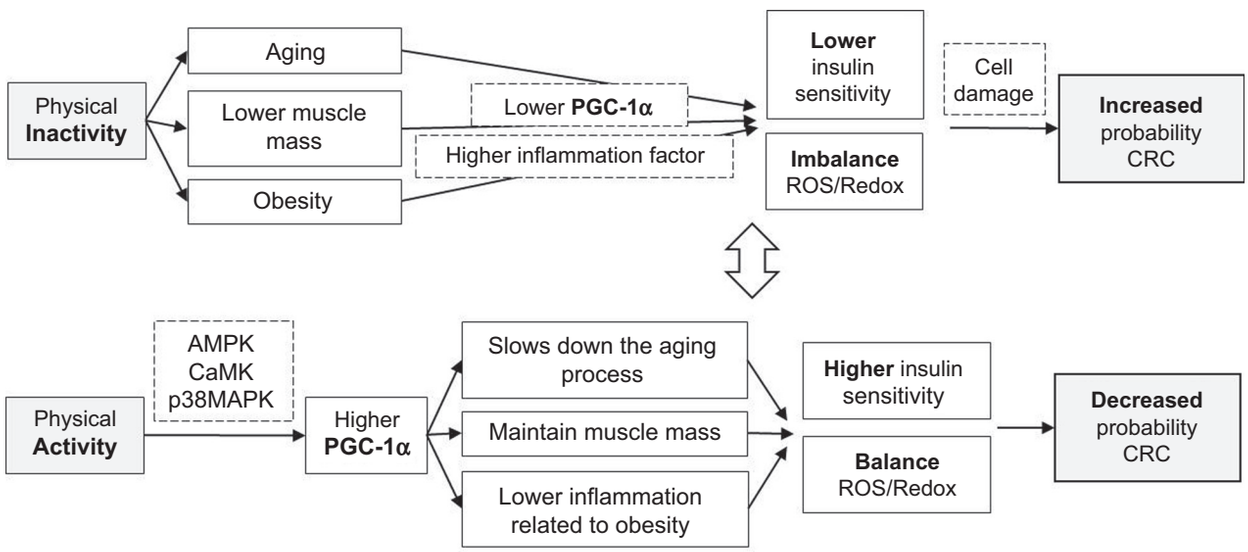

Figure 3.

Insulin sensitivity and ROS/Redox balance as a binding factor among physical activity, PGC-1α, and colorectal cancer. Physical inactivity stimulates the loss of muscle mass, does not contribute to slowing the aging process, and promotes an increase in obesity; it also tends to increase inflammatory factors and tends to be associated with lower levels of PGC-1α, impacting sensitivity to insulin and ROS/Redox balance. This, in turn, promotes cellular damage and increases the likelihood of colorectal cancer. In the opposite direction, physical activity increases PGC-1α and interferes with the sensitivity to insulin and balance ROS/Redox positively, thus reducing the likelihood of colorectal cancer.

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absence of PA, mitochondrial dysfunction, and alterations in the functioning of the insulin hormone will have an opposite effect—an increase of this risk.

On the other hand, ROS is associated with cellular damage that, if not repaired or controlled, contributes to the development of colorectal cancer. *PGC-1α*, although stimulated by ROS and able to increase its production by oxidative phosphorylation, is involved in the regulation of antioxidant defenses, contributing to a good ROS/Redox balance. Therefore, with aging, a decrease in the number of mitochondria and their ability to function can be observed, which leads to a greater accumulation of cellular damage (63, 95). These supposedly increase ROS and alterations in energy production that increase the probability of developing colorectal cancer.

ROS increase may lead to increased proteolysis, autophagy, and apoptosis, contributing to a classic aging or disuse process and significant loss of muscle mass and function (sarcopenia; ref. 63). However, skeletal muscle acts as an endocrine organ, which provides a molecular link between muscles' function and body physiology (70). Thus, the reduction of muscle mass is associated, inter alia, with three main factors: (i) greater resistance to insulin, (ii) the development of a low-grade chronic inflammation state (63), and (iii) poor prognosis in people with cancer or in the process of recovery from this disease (96). At this point, as previously mentioned, *PGC-1α* is associated with a protective role against protein catabolism and the establishment of homeostasis, which reduces loss of muscle mass, protecting against tumor development (63).

Obesity, which is an important risk factor for the development of colorectal cancer, is also associated with the factors just described. In fact, adipose tissue plays a major role in the development of systemic insulin resistance, mostly because of proinflammatory cytokines and macrophages. This resistance might also involve mitochondrial dysfunction in the adipocytes of obese patients (31). Another alteration observed with obesity is an elevated PGC-1α level in the liver and diminished level in skeletal muscle. This tissue-specific pattern of dysregulated PGC-1α activity is predicted to potentially also contribute to systemic insulin resistance, glucose intolerance, and insulin deficiency (85). As in skeletal muscle, where PGC-1α is involved in muscle fiber conversion, it may also be involved in the conversion of mature WAT into brown adipose tissue, where it has been found to coactivate PPARγ to strongly induce *UCP1*. Levels of UCP1 in subcutaneous WAT seem to be dependent on *PGC-1α* expression in response to PA. This suggests that white fat can be converted to a brown fat–like phenotype, that PA has a significant influence on PGC-1α pathways, and that *PGC-1α* may be a novel therapeutic strategy for obesity (31, 97). Physical inactivity increases the likelihood of obesity or worsening of the clinical condition, and it is a risk factor in colorectal cancer development. Therefore, deregulation of energy metabolism with the consequent establishment of low-grade chronic inflammation, with its respective physiologic impacts, seems to be the focus of the theme.

Our study attempted to review an important research area. However, it is limited because it presents many weak associations of fairly isolated observations that could be important.

Future Research

We considered the hypothesis that there is a relationship among *PGC-1α*, PA, and colorectal cancer prevention and verified that there are still many gaps in our understanding of the disease process. It was also emphasized that it is necessary to consider the various pathways and biologic reactions involved; thus, the activated crosstalk processes must be taken into account. The complexities of these pathways and reactions necessitate further studies to provide solid scientific evidence for deeper understanding.

To better understand the role of *PGC-1α* in the protective effect of PA on colorectal cancer, future studies must address the following: (i) which variables related to PA are preponderant in the development of colorectal cancer (e.g., intensity?); (ii) which mechanisms, primary and secondary, are responsible for the beneficial effects of PA in colorectal cancer (*PGC-1α* is a good biomarker; however, it has pleiotropic functions with a wide range of interaction depending on the tissue—a more complete understanding of longevity regulating pathway could be of help); (iii) with regard to the different biologic processes and metabolic pathways in which PGC-1α is involved, which are the most preponderant in the development of colorectal cancer *(PGC-1α*, depending on circumstances, can be a promoter or a protective agent in colorectal cancer, and a better understanding of this is fundamental); (iv) which are the primary and/or secondary pathways in the activation and expression of *PGC-1α* by PA and to which stimulus does it effectively correspond (AMPK, p38MAPK, CaMK, and Akt/protein kinase B are pathways related to PGC-1α; can one of these have more impact with one or another kind of PA? Which one could have a stronger association with colorectal cancer protection?); and (v) what is the impact of *PGC-1α* on colorectal cancer in humans (more studies in humans regarding prevention and therapy could help).

Complementing what has just been described, it seems that if the benefits of PA in colorectal cancer depend partly on *PGC1α* even though they may pass through this gene, they seem to extend beyond it (30). It would be interesting to analyze the role of *PGC-1α* in relation to genes with potential similar properties that were not addressed in this study. An example is *TP53*, which, despite being a well-known tumor-suppressor gene, is being targeted as a modulator of MB and appears to respond to PA stimuli (98).

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Sirtuin 1 is one of the regulators of the longevity pathway interacting with p53, NFκB, Bax, and PPAR and, by deacetylation, activates PGC-1α, which is also influenced by PA (99). Other possible routes of interest are hormonal (thyroid, sexual, metabolic). An example is ERRα (which interacts with PGC-1α) that interacts with receptor 140 (RIP140), a transcriptional coregulator that regulates intestinal homeostasis and tumorigenesis. It has been observed in cellular models and in mice that RIP140 stimulates adenomatous polyposis coli transcription and inhibits the activation of β-catenin, thus has a tumor-suppressor role (100). In addition, among other factors, it may help to form the complex map of interconnection between the different processes that may be involved in the protective mechanism of PA in colorectal cancer.

Conclusions

This study analyzed the protective role of PA in the development of colorectal cancer and existing scientific evidence on the risk factors linked to the biologic processes that are regulated by *PGC-1α* and the effect that PA presents on the activation and expression of this gene. The results of this study create a basis on which future research on the role of this gene can be built on the protective effect of PA on the development of colorectal cancer.

Authors' Contributions

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Cancer Prevention Research

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