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Exercise under hypoxic condition as a potential therapeutic paradigm for digestive system cancers: A narrative review

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Corresponding Author:	Josefa León San Cecilio Hospital, ibs.GRANADA Granada, SPAIN
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	San Cecilio Hospital, ibs.GRANADA
Corresponding Author's Secondary Institution:	
First Author:	Sergio Perez-Regalado, SPORT SCIENCE
First Author Secondary Information:	
Order of Authors:	Sergio Perez-Regalado, SPORT SCIENCE
	Josefa León
	belén feriche
Order of Authors Secondary Information:	
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Suggested Reviewers:	Ginés Viscor Full professor, University of Barcelona: Universitat de Barcelona gviscor@ub.edu expert in hypoxia physiology and practical application
	Prue Cornie Associate Professor, Australian Catholic University Saint Patricks Campus: Australian Catholic University prue.cormie@acu.edu.au Expert in oncology and sport medicine

Opposed Reviewers:	

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Sergio Pérez Regalado (MSc). Department of Physical Education and Sport, Faculty of Sport Sciences, University of Granada, Spain. ORCID: 0000-0001-9503-4286

Josefa León (PhD). Clinical Management Unit of Digestive System, San Cecilio Hospital, ibs.GRANADA, Granada, Spain. ORCID: 0000-0002-0543-4823

Belén Feriche (PhD). Department of Physical Education and Sport, Faculty of Sport Sciences, University of Granada, Spain. ORCID: 0000-0002-3933-6041

Corresponding author: Josefa León (PhD). Clinical Management Unit of Digestive System, San Cecilio Hospital, ibs.GRANADA, Granada, Spain. ORCID: 0000-0002-0543-4823. pepileon@ugr.es

Abstract

Cancer, like other chronic pathologies, is associated with the presence of hypoxic regions due to the uncontrolled cell growth. Under this pathological hypoxic condition, various molecular signalling pathways are activated to ensure cell survival, such as those that govern angiogenesis, erythropoiesis, among others. These molecular processes are very similar to the physiological response caused by exposure to altitude, the use of artificial hypoxia devices (systemic simulated hypoxia) or the delivery of vascular occlusion to the extremities (also called local hypoxia by the blood flow restriction technique). "Tumor hypoxia" has gained further clinical importance due to its crucial role in both tumor progression and resistance to treatment. However, the ability to manipulate this pathway through physical exercise and systemic hypoxia-mediated signalling pathways could offer an important range of therapeutic opportunities that should be further investigated. This review is focused on the role of systemic hypoxia combined with exercise as a potential therapeutic proposal in digestive system neoplasms. We conclude that there is evidence that exercise performed under hypoxic conditions can improve digestive system cancers modulating prognosis and quality of life, which could be considered as a potential new intervention in digestive oncological population.

Keywords: aerobic exercise, cell hypoxia, digestive system neoplasms, exercise, hypoxia, resistance training.

Key points:

- Systemic hypoxia exposure operates as the main regulator of haematological, angiogenic, metabolic and neural adaptations.
- The physiological effect of systemic hypoxia exposure contributes to vascular remodelling that could reduce the local hypoxia of the tumor microenvironment and decrease the leakages in the vascular wall making the tumor more vulnerable to anti-tumor treatment and immune system action.
- Although further research focused on the main topic is needed, a wide spectrum of new possibilities support the exercise performed under hypoxic conditions as a new potential therapeutic intervention in digestive oncological population.

Introduction to digestive system neoplasms

Cancer is a disease in which genetic and/or epigenetic changes drive abnormal cell growth in a way that is deleterious to the organism (1). Immunosuppression, a sedentary lifestyle, old age, chronic debilitating disease, previous use of chemotherapy and abuse of some drugs (such as analgesics, antibiotics and corticosteroids) increase cancer risk (2).

This disease is usually classified according to the characteristics of the tumor itself, as well as the location and organ affected. Digestive system cancer encompasses seven variants of malignancies derived from the organs that make up the digestive system (3, 4). According to global cancer statistics, only lung cancer is more prevalent than colorectal cancer, a digestive cancer in the top five causes of cancer-associated mortality worldwide (5).

Numerous treatments are used to treat gastrointestinal cancers, but many are invasive and/or cause side effects. Regular exercise has been linked to a lower risk of digestive system cancer development (6, 7). Considering the sequelae of cancer and its treatments, this practice is also emerging as a non-invasive colorectal cancer modulator therapy. In fact, many reports support the beneficial effects of exercise in cancer patients. Specifically, Devin et al. demonstrated that acute high intensity interval exercise transiently reduces cell growth in patients with colorectal cancer (8). Another review concluded that regular exercise reduces body fat and regulates insulin levels, modulating colorectal cancer progression (9).

Supporting this idea, new evidence is suggesting the positive effects of exposure to systemic hypoxia at rest or during exercise on angiogenesis, mitochondrial biogenesis and promotion of skeletal muscle fiber type I transition (7, 10). Unfortunately, there is insufficient data to determine how exercise performed under hypoxic conditions could modulate the development of digestive system cancers. From this perspective, we discuss recent reports about the modulation of digestive system cancer by exercise from a molecular point of view, targeting future potential treatments linking exercise programmes with systemic hypoxia.

Cancer metabolism and tumor microenvironment

Cancer cells adapt their metabolism to obtain the energy necessary to support their growth (11). In the 1920s, Otto Warburg first described increased glucose metabolism in cancer cells, even in the presence of oxygen, with marked lactate production, which was interpreted as mitochondrial dysfunction (1, 12). Actually, it is now known that mutations in genes responsible for mitochondrial metabolism are crucial for tumour cell survival and proliferation in an environment with limited resources (13). Mutations in genes of the mitochondrial tricarboxylic acid cycle (TCA), such as succinate dehydrogenase (SDH), fumarate hydratase (FH), and isocitrate dehydrogenase 1 (IDH1) and 2 (IDH2) have been well studied (Fig. 1) (1).

SDH, complex II (CII) of the electron transport chain (ETC), is composed of four encoded subunits and contributes to electron transfer (14). SDH is also part of the TCA, catalysing the oxidation of succinate into fumarate (15). Genetic defects in SDH lead to mitochondrial complex II activity inhibition and succinate accumulation, which blunt prolyl hydroxylase (PHD) activity and reactive oxygen species (ROS) generation. Similar effects are found in the mutation of FH genes (16). Fumarate is an oncometabolite and its accumulation suppresses α-KG-dependent dioxygenases, inducing hypoxia-inducible transcription factor-1α (HIF-1α) stabilisation. Also, depletion of FH increases the dissociation, nuclear translocation and activity of nuclear factor (erythroid-derived 2)-like 2 (Nrf2) and increases the transcription of antioxidant and oncogenic genes, promoting tumor survival (14, 17, 18). Finally, FH mutation contributes to epithelial to mesenchymal transition (EMT), mainly by suppressing miR-200 and E-cadherin expression, and also promoting Twist1 and vimentin expression (14). Next, IDHs catalyse the oxidative decarboxylation of isocitrate to produce 2-oxoglutarate (α-KG). Conversely, mutant IDHs metabolise α-KG into 2-hydroxyglutarate (2-HG). The tumorigenic activity of 2-HG has been linked to a suppressive effect of PHDs, αKG-dependent histone and DNA demethylases, enhancing HIF-1α activity (19, 20).

[Insert *Figure 1*]

HIF are a group of DNA-binding proteins that induce transcription of numerous genes involved in angiogenesis, glycolysis, metabolic adaptation, erythropoiesis and cell survival. They are heterodimeric transcription factors composed of α and β subunits. HIF-1α is directly regulate by oxygen levels (gradual increase from 20 to 5% O_2 and a pronounced increase below 5% O_2) as well as a master controller of the transcriptional response to systemic hypoxia (21, 22). Three distinct genes are known to encode the HIF-α subunit in mammals: HIF-1α and HIF-2α, which function as transcriptional regulators and have unique and overlapping target genes, and HIF-3α, whose role is less well understood. Acute adaptation to hypoxia is governed by HIF-1α (< 24 h), promoting initial angiogenesis. In normoxia, HIF-α degrades rapidly, while in hypoxia it stabilises, translocates to the nucleus, and dimerises with HIF-β subunits (present independently of partial pressure of oxygen (PaO_2)) to form HIF-1. HIF-1α binds to hypoxia-sensitive elements of HIF-1 target genes and stimulates protein synthesis by regulating the transcription of genes involved in the control of erythropoiesis, angiogenesis, vasodilation, energy metabolism, apoptosis and synthesis of catecholamines (23). When exposure to systemic hypoxia becomes chronic (> 24 h), HIF-1α levels progressively decrease and HIF-2α and HIF-3α begin to be expressed in the human endothelium, favouring further development of the vascular network (24). Overexpression of HIF-1α in the tumor microenvironment (TME) contributes to cancer progression and promotes tumor cell adaption, even in the presence of oxygen. Then, HIF-1α plays a critical step in cancer survival and growth by modulating the activity of several metabolic enzymes of glycolysis, supporting the reprogramming of glucose metabolism in cancer cells (21, 25).

In terms of neoplasm development, continuous tissue growth that exceeds the available resources implies the activation of angiogenic mechanisms that provide nutrients, oxygen and waste removal (26). The intrinsic local hypoxia of a tumor triggers a response through HIF-induced pro-angiogenic factors, including vascular endothelial growth factor (VEGF), which is the master regulator of the angiogenesis process and is also involved in endothelial proliferation (27, 28). This unbalanced proangiogenic response is characterised by an uncontrolled and faster growth rate than seen in a normal endothelial cell, creating a chaotic and abnormal network of blood vessels. (29). Tumor vessels are disorganised and leaky due to structural failures, which allow the extravasation of intravascular fluid and proteins into the interstitial fluid, increasing the internal pressure (30). As a result, the blood supply is not homogeneous throughout the tumor and local hypoxic regions develop.

Conversely, the collapses generated in this TME act as a shield against the immune response and drug administration (31, 32).

Particularly in hypoxic cancer cells (Fig. 1), HIF-1α upregulates glucose transporter-1 (GLUT1), promoting glucose uptake into tumor cells, and hexokinase-2 (HK2), an enzyme that generate glucose 6-phosphate (G-6-P) by glucose phosphorylation (21). Furthermore, HIF-1α also contributes to the maintenance of cellular homeostasis by mediating pyruvate dehydrogenase kinase 1 (PDK1) expression. PDK1 reduces the conversion of pyruvate into acetyl-coenzyme A through pyruvate dehydrogenase (PDH) inhibition (33). Additionally, the HIF-1α-inducible enzyme lactate dehydrogenase A (LDHA) metabolises the accumulated pyruvate to produce lactic acid, and monocarboxylate transporter 4 (MCT4) removes the lactate from cancer cells (34, 35). Nevertheless, this ejected lactate is taken up by normoxic cancer cells through MCT1 (36). These normoxic tumor regions convert lactate into pyruvate through lactate dehydrogenase B (LDHB) as an energy source for the TCA cycle, reducing glucose consumption and promoting its diffusion distance (37, 38). As a result, a feedback loop is established, through which the hypoxic tumor regions can evade the immune system and anti-tumors treatment, and also achieve a continuous supply of nutrients coming from the normoxic tumour regions.

However, hypoxic cancer cells, due to their elevated lactate production, show an increase in hydrogen ion (H^+) concentration leading to an acidic intracellular pH (pHi). This is a crucial point in the progression of the tumor, increasing the expression of HIF-1α-dependent genes in order to restore pHi levels (39). This is achieved through activation of CA9 carbonic anhydrase IX (CAIX) by HIF-1α, which promotes bicarbonate and H^+ formation from released CO_2, and activation of sodium-hydrogen exchanger 1, which exchanges intracellular H^+ for extracellular sodium ions (39, 40). As a consequence, lactate and protons accumulate and acidify the extracellular space, acting as another obstacle to the effectiveness of radio- and chemotherapy (41).

There is growing evidence on cancer cell survival under hypoxic intracellular conditions. On one hand, many authors defend an adaptation process, showing less exposure to ROS through a HIF-1α-dependent mechanism known as autophagy (42). Poor oxygen supply results in HIF-1α stabilisation, mediating a signalling pathway response involving Bcl-2/adenovirus E1B 19-kDa interacting protein 3 (BNIP3) and BNIP3-like protein

(BNIP3L) activation. BNIP3 and BNIP3L increase beclin1 release, which in turn leads to a switch to autophagy (43). On the other hand, cells may become adapted according to their resource availability due to adenosine monophosphate-activated protein kinase (AMPK) activity. AMPK is an energy sensor that triggers autophagy, promoting UNC-51-like kinase 1 (ULK1) activity and suppressing the mTOR pathway (43, 44). This process allows the removal of defective mitochondria without releasing cytochrome C, which would induce cell apoptosis (42). Lastly, toxic damaged proteins and organelles are processed and re-utilised for macromolecule biosynthesis (40, 45).

The influence of the chaotic vascular physiology on the hypoxic tumour microenvironment development

Tumor growth and development depends on the availability of nutrients and oxygen. A resource-poor environment implies the activation of mechanisms, such as angiogenesis, that allow the tumor to survive. Unlike healthy tissue, tumor angiogenesis is characterised by an overabundance of pro-angiogenic factors, including VEGF, basic fibroblast growth factor (bFGF), transforming growth factor β (TGFβ) and tumor necrosis factor alpha (TNF-α), resulting in a disorganised, leaky and immature network of blood vessels (46, 47). Despite the chaotic vasculature, this provides a hypoxic and acidified ecosystem that allows the tumor to evade the immune response and antitumor treatment (48).

In this context, several mechanisms upregulate the expression of VEGF, which is a key mediator of angiogenesis, through the activation of various signalling pathways involved in initiating angiogenesis and the creation of new blood vessels (49). A recent review shows a relationship between the upregulation of VEGF and its receptors and colorectal cancer development in humans (50). Overexpression of VEGF also promotes vascular permeability and upregulates the expression of angiopoietin-2 (ANG2) in colorectal cancer (51). Thus, ANG2 inhibits ANG1, destabilising the interaction between endothelial cells (EC) and vascular pericytes (52). Additionally, ANG2 increases interleukin-10 (IL-10) release by interaction with TIE2-expresing monocytes (TEM) (53). Both IL-10 and VEGF contribute to the inhibition of T cell function, modulating the $CD4^+/CD8^+$ ratio and the maturation process of dendritic cells (DCs) (47, 54). In fact, 8 weeks of moderate resistance training (3 × 12 rep, 60% repetition maximum (RM)) in normoxia augmented blood VEGF and ANGP-1

concentration in a young healthy population (55). Another study conducted with young healthy participants showed an increase of the interstitial VEGF content after 4 weeks of high-intensity intermittent cycling training (24 × 1 min, 3 times/week; 117% VO_{2max}) (56). Moreover, VEGF expression is involved in platelet-derived growth factor (PDGF)-dependent PDGFRβ activation, promoting the recruitment process of pericytes by tip endothelial cells. Several studies show that high physiological concentrations of VEGF-A can competitively inhibit PDGF activity through direct binding of VEGF-A to PDGFRβ (57-59).

In addition, VEGF also compromises the stability of the endothelial wall by modulating the activity of vascular endothelial cadherin (VE-cadherin) (30). VE-cadherin is specifically expressed in endothelial cells and plays an essential role in promoting endothelial junctions and the integrity of blood vessels (60). Several growth factor receptors modulate the VE-cadherin signalling pathway, including VEGFR2. Stimulation of VEGFR2 by VEGF leads to Src kinase family phosphorylation at the Y658 and Y731 residues, thereby disrupting VE-cadherin-associated protein junctions (61, 62).

Exercise as a potential anti-tumor therapy

Continuous physical activity/exercise programmes have been attracting more attention as an antitumor regulatory mechanism, in addition to improving the response to treatment. A recent study associates the effects of leisure-time physical activity with a lower risk of developing 13 different types of cancer (63, 64). Moreover, in the past two decades, physical exercise as a co-adjuvant therapy has played an important role in improving cancer survivors' outcomes. Increased evidence shows significant advances regarding better prognosis that correlate exercise with systemic effects, for example remodelling of blood vessel networks and metabolic alterations (65, 66). Another recent study shows that regular aerobic exercise reduces levels of adhesion molecules involved in colon cancer growth and development (67). Many of these effects are due to a positive modulation of the physiological TME.

It is well stablished that physical activity is associated with an increase in perfusion by arterial pressure modulation. Alterations in arterial pressure trigger a modified shear stress and transmural pressure response,

leading to circumferential strain due to the nature of arteries. In response to cyclic circumferential strain, endothelial cell mechanosensors transform the mechanical stimuli into a chemical signal, leading to the activation of several signalling cascades (68, 69). Consequently, production of nitric oxide (NO) and Ca^{2+}-dependent prostaglandin I_2 (PGI_2) is enhanced in endothelial cells and these substances are released into smooth muscle cells (SMCs). NO and PGI_2 activation modulate Ca^{2+}-opening channels and myosin light chain kinase (MLCK) activity, promoting SMC vasodilation (70, 71). Aerobic exercise triggers perfusion and vascular remodelling, which facilitates drug delivery and immune system activity to combat tumor development and growth (72). Thus, several studies conclude that chronic aerobic exercise promotes vessel maturity and perfusion in murine breast and prostate cancer, reducing tumor hypoxia and improving chemotherapy efficacy (73, 74). Moreover, another study shows an anti-angiogenic role of secreted protein, acidic and rich in cysteine (SPARC), reducing VEGF expression in colon cancer (75).

[Insert *Figure 2*]

In response to exercise (Fig. 2), SPARC is released from the muscle tissues into the bloodstream and is associated with intercellular interaction, cell differentiation, and also acts as a potentially anti-tumorigenic myokine in a colorectal cancer model (76). In fact, Aoi et al., showed that after 4 weeks of an aerobic exercise programme (30 min, 70% VO_{2max}, 3 times/week), working muscles secrete SPARC, inhibiting colon tumorigenesis via an apoptosis-dependent mechanism. This study also revealed that a single training session was enough to immediately increase plasma SPARC levels, which returned to basal levels 6 hours post-session (77). Although the role of SPARC in response to exercise is well established in colorectal cancer, the molecular mechanism and mediators implicated need further study (78).

Physical exercise also has a regulatory effect on immune system efficacy, and consequently in cancer modulation. Natural killer (NK) cells are the most responsive immune cells to exercise (78). It has been shown that high NK cell concentration in the TME is a positive prognostic factor in gastrointestinal sarcoma, and gastric and colorectal cancer patients (79, 80). However, under the local hypoxic tumor microenvironment, HIF-1 expression seems to reduce NK activity by promoting shedding of MICA (an activating receptor found

in NK and CD8+ T-cells), which reduces the ability of NK cells to recognise malignancy in breast and colon adenocarcinoma (81, 82). A recent study has displayed a significant increase in NK cell infiltration in tumors after a voluntary running protocol in mice. This result associates the effects of exercise with improved mobilization and redistribution of NKs due to exercise-induced IL-6 and epinephrine release in lung and liver cancer models (78, 83). Additionally, even though hypoxia is known to enhance the pro-inflammatory response, exercise mediates the upregulation of various myokines, such as IL-6, which re-establishes the anti-inflammatory balance through HIF1-α activity (84, 85).

Moreover, in colorectal cancer survivors, exercise-induced physical adaptations regulate tumour metabolism by reducing intratumoral lactate concentration, thereby contributing to the interruption of the vicious cycle that facilitates tumor growth and immune system evasion (86). It has been demonstrated that regular exercise improves CD8+ T-cell antitumoral efficacy by interaction with skeletal muscle-derived metabolites such as lactate, in a colon cancer model (87). Additionally, recent research supports an enhanced CD8+ T-cell response due to the relationship between exercise and suppression of HIF-1α activity (88). Finally, regular practice of physical exercise contributes to the enhancement of anti-tumor immunity, inducing a phenotypic shift in tumor-associated macrophages (TAMs) from M2 to M1 (89). M1 macrophages increase the cytotoxic T cell (CTLs)/regulatory T cell (T_{reg}) ratio, which stimulates pro-inflammatory mechanisms, promoting a cytotoxic anti-tumor response (78, 90).

Exercise and digestive cancer

Table 1 shows an overview of the results obtained in systematic reviews published in the last two years relating the role of exercise and its influence on colon cancer patient's prognosis. Aerobic exercise stands out as the most used type of exercise over resistance and high intensity interval exercise; however, positive results were also observed in both modalities. Although there are a wide range of protocols and it would be difficult to establish an exact exercise dose, certain patterns can be observed that lead to several positive consequences on patient prognosis (aerobic training: 150-300 min/week, 50-75% HRmax; resistance training: 10-15 reps, 65-75% 1RM; high intensity interval training: 60-300 min/week, 50-75% HRmax). Considering the above-

mentioned points, this table show strong positive evidence mainly on muscle and metabolic function. Furthermore, they show different clinical implications, mainly related to improvements in the quality of life (sleep quality, subjective pain scale, mental fatigue or motivation), as well as biomarkers linked to the maturity of vascular structure (sICAM-1) and antitumor-related biomarkers (91, 92).

[Insert *Table 1*]

Exercise under hypoxic conditions & digestive cancer: what little is known

In order to explore the potential use of physical exercise under hypoxic conditions in patients with any type of digestive cancer an exhaustive search was carried out using the online databases Medline (via PubMed), Scopus, Web of Science (WOS) and Cochrane Library, including the terms "exercise", "digestive cancer" and "hypoxia" (see *Supplementary material*). Unfortunately, the scientific literature about this topic is quite scarce and the effect of the type and severity of the hypoxia, at rest or combined with different types of exercise, on this oncological population has not been studied yet. Despite this, we have reviewed the current knowledge on the topic and formulated a reasonable hypothesis about the potential benefit that exposure to hypoxia could have on the treatment and prognosis in patients with digestive cancer.

Nowadays, hypoxia is well established as an important resource in the optimization of sports performance, especially in high-level athletes. Additionally, it is an essential element in the preparation of athletes who compete over 1500 m. Athletes benefit from the stimulus caused by hypoxia generating a positive effect on their performance both whilst at altitude and after their return to sea level (93). Currently is not necessary to physically be at altitude in order to generate the main physiological changes induced by hypoxia (94). There are artificial hypoxia devices (masks, tents and hypoxia rooms), which generate "systemic normobaric hypoxia" by reducing the FiO_2 (95), providing easy access to this environmental condition to all populations. To reduce the adverse effects that sometimes occur in chronic hypoxia, intermittent hypoxia training emerges as an alternative strategy that promotes physiological adaptations produced during the hypoxic acclimatization, such

as the haematological or ventilatory. (96). Intermittent hypoxia is defined as the repetitive interchange of episodes of hypoxia and normoxia. The cumulative effect begins with the first exposure to hypoxia (97).

The most sought-after physiological adaptations are hematological, due to their potential link to long-term test performance. Other adaptations that affect central (e.g. neural adaptations) and peripheral (e.g. mitochondrial activity) systems also seem to largely lead to improvements in performance, even when hematological adaptations do not occur (98). Moreover, the ascent in altitude is presented as a potential opportunity to enhance muscular strength, power explosiveness and trainability due to alterations in pattern recruitment associated with the accumulation of anaerobic metabolites during exercise under these conditions, as well as the reduction in air density (99).

[Insert *Figure 3*]

Different types (natural or simulated), strategies (e.g. at rest or combined with exercise; intermittent or continuous exposure) and severities of hypoxia (altitude or the equivalent FiO_2 from 1500 to 5500 m asl) are frequently combined. In all of these settings, systemic hypoxia exposure triggers a reduction in tissue FiO_2 that causes a cascade response from affected systems in the body, including the HIF-1α signalling pathway (100). The balance of the HIF expression response induced by systemic hypoxia and the level of expression of intratumoral HIF-1α determines the effectiveness of the adaptation and thereby, the potential therapeutic applications (Fig. 3). Therefore, the mechanism induced by systemic hypoxia through the expression of HIF-1α and/or HIF-2α is a crucial point in the regulation of tumor growth and depends on the mutational landscape of tumor cells (101, 102). This includes the availability of required cofactors, as well as the functionality of specific pathways of the HIF-α isoform, such as apoptosis (primarily driven by HIF-1α) or cell cycle progression (primarily driven by HIF-2α) (103).

As occurs during pathological conditions, the signalling pathways activated by the physiological response to the ascent in altitude or breathing of oxygen-depleted air are also largely regulated by the activation of HIF-1α expression. Sport training under systemic hypoxia exposure has been demonstrated to improve cardiorespiratory and metabolic function in both trained and untrained healthy people (104, 105). These benefits

involve the regulation of gene transcription by HIF-1α, promoting important functions such as erythropoiesis, angiogenesis, vasodilation, energy metabolism, apoptosis and catecholamine synthesis (7, 23). Exercise perse, induces alterations in mitochondrial biogenesis and activates several transcription factors in myofibers promoting angiogenic processes VEGF-dependent improving vascularization through vessel sprouting and splitting (106). Nevertheless, when exercise is combined with periods of exposure to hypoxia, the consequence physiological effect is more remarkable as shown Aleksandra Żebrowska et al. This study assessed the acute effect of exercise under normobaric hypoxia and obtained a depletion of glycemia levels and a regulation on biomarker levels related to prevent diabetes cardiovascular complications (107). Another recent study, twelve healthy males performed four tests to exhaustion in different conditions (normoxia, 2000 m, 3000 m and 4000 m above sea level) showing improvements up to 2000 m condition on the bioavailability of angiogenic, extracellular matrix-related biomarkers (108). The main mediators of these molecular changes include the PGC-1α, HIF1-α, and VEGF responses, which are linked to the exposure to hypoxic conditions (109).

In recent decades, several studies have also supported therapeutic uses of hypoxia, at rest and/or combined with exercise in many pathological areas. Moreover, the exploration of non-pharmacological treatments based on hypoxia-induced angiogenesis can be considered as a successful strategy in various pathologies, and even in the treatment of some types of cancer (110). For instance, a recent review shows numerous positive effects of intermittent systemic hypoxia exposure supplied at rest conditions in patients with neurological dysfunction, obesity, coronary artery disease, hypertension or bronchial asthma (111, 112). Another study in a healthy sedentary population that performed 4–5 rest exposure sessions to intermittent systemic hypoxia /week (target SpO_2: week 1: 95%, week 2: 90%, week 3: 85%, and weeks 4 and 5: 80%) showed an increase in the parasympathetic contribution to the sympathovagal balance of the heart and a possible improvement in systolic blood pressure and some fitness parameters (113). Furthermore, Pesta et al. in healthy young sedentary population showed that after 10 weeks of a strength and endurance training programmes (3 sessions/week; intermittent systemic hypoxia [FiO_2: 13.5%]), there were improvements in fatty acid oxidation capacity due to qualitative mitochondrial changes in both strength and endurance hypoxic groups (114). Nishiwaki et al. in active postmenopausal women showed an association between 8 weeks of an aquatic exercise programme (30 min/day; 4 days/week; 50% VO_2max) under intermittent systemic hypoxic conditions (FiO_2: 16.5%) and a

reduction in arterial stiffness and vascular remodelling (115). In patients with obesity, an improvement in fitness condition and lower mechanical work and joint stress was associated with prolonged exposure to natural hypoxia (8 weeks; 90 min at 60% of the heart rate at maximum aerobic capacity, 3 days/week; FiO_2 = 15%) (116). Hypoxia-induced appetite reduction has been shown to occur due to hormonal regulation and an increase in energy expenditure (117, 118). Another crucial area of study for disease treatment is the therapeutic use of stem cells and how they work due to their ability to differentiate into any cell of an organism and have the ability of self-renewal (119). Although the exact mechanism of HIF1-α and HIF-2α in stem cell survival (both under normal and pathological conditions) is not known, HIF-1α appears to be the main regulator of normal and neoplastic stem cells in all types of hypoxia (120). The upregulation of HIF-1α favors the treatment of ischemic pathologies (121), while its reduction in tumor-specific regions could lead to the inhibition of tumor growth (122, 123). In this context, miRNAs could provide therapeutic possibilities by modulating the HIF switch, aiming to improve physiological and pathophysiological conditions (124).

In cancer, exercise performed in normoxia is considered to be a potential inhibitor of cancer progression that regulates vascular maturity and improves intratumoral perfusion. It is also known to reduce the local hypoxia of tumor structures and enhance the antitumor immune response, thereby improving the efficacy of treatment and the quality of life of patients in a wide range of cancer types (64). Physiological adaptations associated with physical exercise are potentially larger when accompanied by exposure to systemic hypoxia (125). Furthermore, some pharmacological strategies have emerged targeting the HIF1-α signalling pathway (126). A recent review summarises HIF-1α inhibitors in microenvironmental regions of tumor hypoxia as a potential anti-tumor treatment, promoting apoptosis and reducing proliferation and angiogenesis (127). HIF-1α intratumoral overexpression is associated with a poor prognosis in various solid cancers, including gastric and colon cancer (128). Results from Ioannou et al. also supported the key role of HIF-1α in tumor angiogenesis and progression in colorectal cancer patients (129). Despite this evidence of the negative intratumoral role of HIF1-α in cancer progression, some studies show numerous physiological benefits when patients are exposed to systemic hypoxia (130). Along with the modulatory effect of HIF on angiogenesis and apoptosis, even physical exercise combined with simulated environmental intermittent hypoxia exposure at rest is also associated with mobilisation of NK cells and pro-antioxidant balance improvements in cancer patients (131).

Conclusion

In this review, we focus on the role of systemic hypoxia combined with exercise as a potential therapeutic proposal in digestive cancer. We aim to highlight the crucial role that systemic hypoxia plays in athletic performance, where it operates as the main regulator of haematological, angiogenic, metabolic and neural adaptations. On one hand, numerous studies support the effectiveness of exercise programmes in the modulation of tumor development and growth in many types of cancer. Furthermore, the literature shows that systemic hypoxia exposure alone contributes to counteract the negative symptoms in cancer, in a wide range of conditions, although this effect seems to be intensified when hypoxia is combined with an exercise programme. This is partly explained by the vascular remodelling that reduces the local hypoxia of the TME and decreases leakages in the vascular wall. This action makes the tumor more vulnerable to anti-tumor treatment and immune system action. Therefore, the effect is determined by the balance of the HIF expression response induced by the systemic hypoxia and the intratumoral HIF-1α/HIF-2α ratio. On the other hand, systemic hypoxia also affects specific cytokines that play crucial roles in tumor growth, such as IL-6 in liver cancer and SPARC in colorectal cancer. Considering the beneficial physiological effects of systemic hypoxia exposure documented in this review, a wide spectrum of new possibilities arises for modulating prognosis and quality of life in digestive oncological population. Nevertheless, further research focused on exercise programmes under systemic hypoxic conditions in digestive cancer models is needed to determine how to utilise the potential effects of exercise in hypoxia on patient prognosis, opening an unexplored non-pharmacological research area.

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Figure legend

Fig. 1. Schematic representation of the consequences (discontinuous green arrows) of mutation of genes (red squares) involved in different processes in a hypoxic cancer cell. *GLUT1, glucose transporter-1; HK2, hexokinase-2; PDK1, pyruvate dehydrogenase kinase 1; MCT4, monocarboxylate transporter 4; ROS, reactive oxygen species; LDHA, lactate dehydrogenase A; Nrf2, (erythroid-derived 2)-like 2; Keap1, Kelch-like ECH-associated protein 1; 2-HG, 2-hydroxyglutarate; PHD, prolyl hydroxylase; SDH, succinate dehydrogenase; FH, fumarate hydratase; IDH2, isocitrate dehydrogenase 1; PDH, pyruvate dehydrogenase; HIF-1α, hypoxia-inducible transcription factor; CI-V, electron transport chain complex I-V.* Red lines, inhibition; black arrows, healthy cellular process.

Figure 2. In response to exercise, several myokines are released into the bloodstream (A). On the one hand, the joint action of IL-6, epinephrine and SPARC promotes an anti-tumour response (B). On the other hand, shear stress-dependent signalling pathways trigger an angiogenic response leading to vascular remodelling and reduces the local hypoxia of the tumor microenvironment (C). This increases tumour vulnerability and the effectiveness of the anti-tumour treatment and immune system action. *SPARC, secreted protein, acidic and rich in cysteine; IL-6, interleukine-6.*

Figure 3. The rapid depletion of nutrients and oxygen levels results in a favourable atmosphere for triggering several signalling pathways necessary for tumour survival. Acute microenvironment hypoxia caused by rapid tumour growth promotes the induction of both HIF-1α and HIF-2α. On the one hand, HIF-1α reduces hypoxia levels through activation of angiogenesis and/or the reperfusion process or even cell death. Alternatively, chronic hypoxia can increase HIF-2α levels, promoting tumour adaptation, proliferation and progression. *HIF-1α, hypoxia-inducible transcription factor-1α; HIF-2α, hypoxia-inducible transcription factor-2α.*

Figure 1

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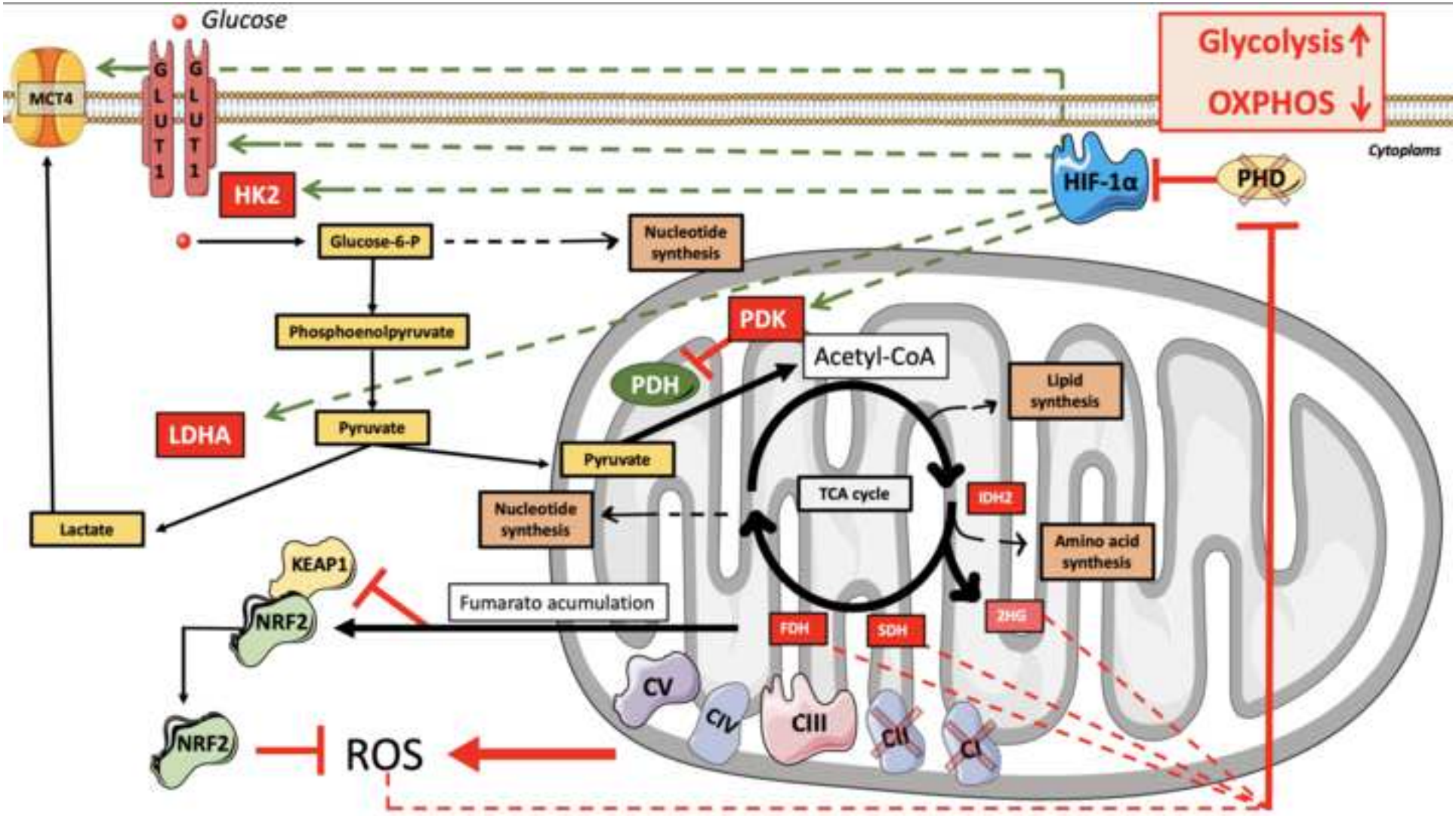

Figure 2

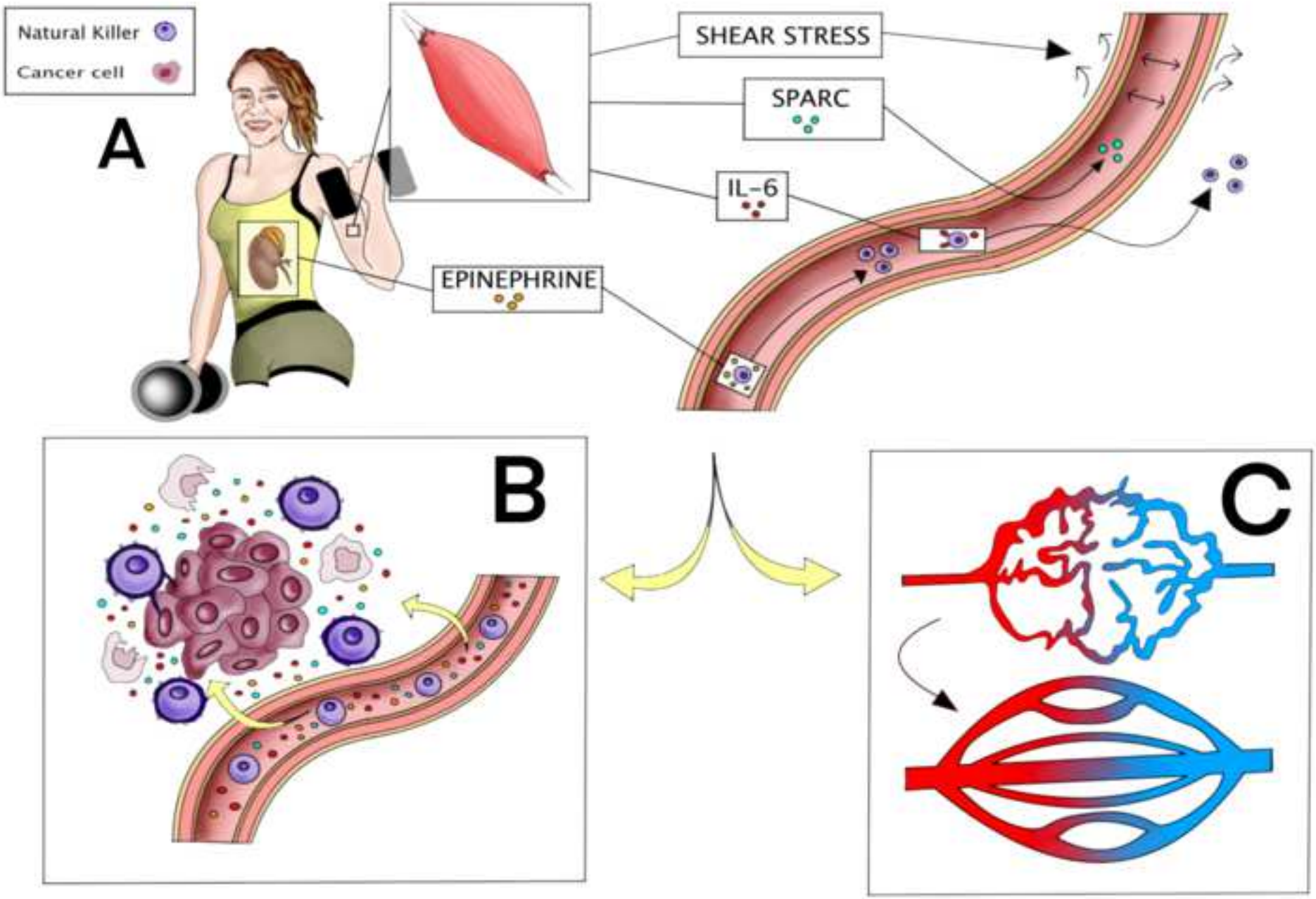

Figure 3

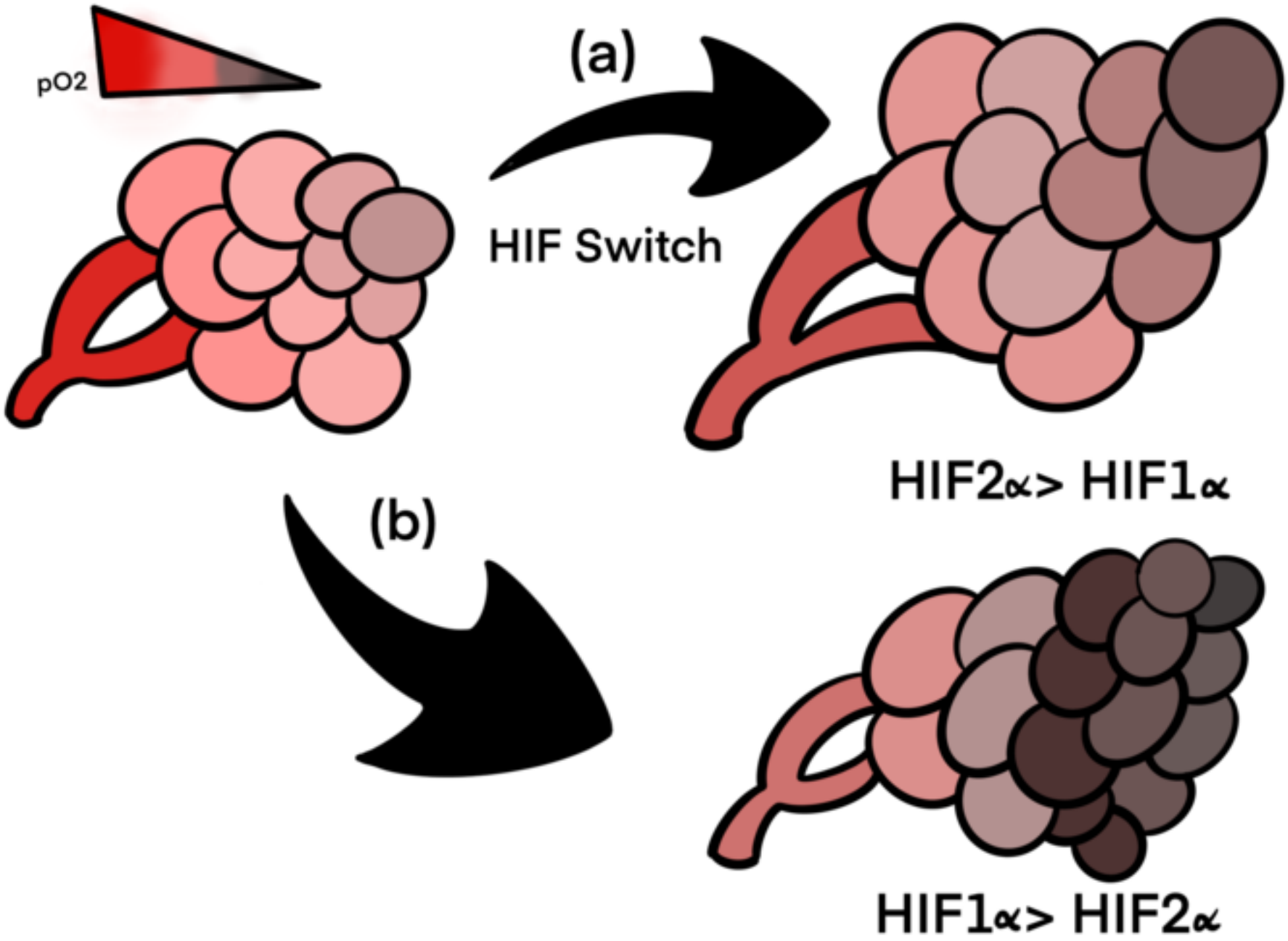

Table 1

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Table 1. Overview of systematic reviews published in the last two years linking the role, doses and type of exercise and colon cancer development.

Author's	**Digestive Cancer**	**Type of patient** *(intervention vs. control group)*	**Exercise Protocol**	**Type of exercise**	**Duration (weeks)**	**Main results**	
						Physical condition	**Clinical implications**
Dun L, et al., 2020 [90]	Colorectal cancer	Cancer survivors (n=39; control, low-dose & high-dose exercise)	150 min/week or 300 min/week (50%-70% of age- predicted HRmax)	Aerobic exercise (treadmill-walking)	24	Only 300 min/week program physical function ↑	Only 300 min/week program improves multiple of health-related quality of life (HRQoL) ↑ Sleep quality and fatigue ↑
		Cancer patients (n=45; control & supervised exercise)	2 s/week (40-60 min/session) 40-75% RPE.	Aerobic/ resistance training	12	Cardiorespiratory fitness ↑ Physical activity ↑	Subjective pain scale ↓
		Cancer patients (n=33; control & supervised exercise)	Aerobic program 150min/week: interval training based on HR at ventilatory threshold (3x2 min up to 2x7 min) and below (3x4 min up to 1x7 min). Muscle strength training 2 s/week: 2 × 10 rep (65% RM) up to 1 × 10 rep (75% RM) and 1 × 20 rep (45% RM) at the end of the program. Outcome assessment at baseline, 18-weeks and at 36-weeks postintervention.	Aerobic/ resistance training	18	VO_2max ↑ Peak power output ↑ VO_2peak (18 and 36 week) ↑	Significant reduction in physical fatigue at 18 week and general fatigue at 36 weeks Mental fatigue, reduced motivation and reduced activity ↓
Gao R, et al., 2020 [91]	Colorectal cancer	Cancer colorectal survivors	14 studies [3-7 s/week (60 to 300 min/week)]	Aerobic and high-intensity interval exercise	6-48	***Physical function:*** VO_2peak ↑ ***Body composition:*** lean mass ↓ & fat mass ↑ ***Metabolic growth factors:*** fasting insulin levels and insulin resistance ↓	Increase metabolism, and tumor-related biomarkers that promotes anti-tumor chemotherapy effect. ***Biomarkers:*** sICAM-1 levels ↓ Proinflammatory immune ratio ↓ and oxidative DNA damage ↑
			2 studies [3s/week; (10 min 50-70% HRmax + 4 min 85-95% HRmax + 3 min 50-70% HRmax) x 4 reps)].	Alternating moderate & high-intensity	3-8		
			3 studies [30-40 min/day; 7 s/week 50-60% VO_2max]	aerobic exercise moderate-intensity and resistance training	12		
			6 studies [aerobic exercise: 3s/week (90-270 min/week) and body weight resistance training (3-7 s/week)].	Aerobic & resistance exercise	6-24		

	4 studies [aerobic exercise (20-30 min, 3-5 s/week [65-75% VO_2max] and (3x5 aerobic exercise [30 min/day]) and resistance exercise (3x15 reps for 7 core exercises)]	Aerobic & high-intensity resistance training	6-12 & 16 weeks
	1 study [(3s/week) including running/walking (90 min) and stabilization core exercises (8/12 rep)].	moderate-intensity resistance training	8 weeks

↑ = increase; ↓= decrease; rep= times to repeat; s= train session; HR= heart rate; RPE= rated of perceived exertion; sICAM-1= soluble intercellular adhesion molecule-1, 1 RM= 1 repetition maximum.