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HORMONES, CANCER AND PHYSICAL EXERCISE: MOLECULAR INTERACTIONS, SYSTEMIC RESPONSES AND TRANSLATIONAL PERSPECTIVES

HORMÔNIOS, CÂNCER E EXERCÍCIO FÍSICO: INTERAÇÕES MOLECULARES, RESPOSTAS SISTÊMICAS E PERSPECTIVAS TRANSLACIONAIS

HORMONAS, CÁNCER Y EJERCICIO FÍSICO: INTERACCIONES MOLECULARES, RESPUESTAS SISTÉMICAS Y PERSPECTIVAS TRASLACIONALES

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ABSTRACT
This chapter presents a comprehensive overview of the interactions between hormones, carcinogenesis, and physical exercise, addressing biochemical and molecular foundations as well as translational applications. It first highlights that sex steroid hormones (estrogen, testosterone), metabolic hormones (insulin, IGF-1), and adipokines (leptin, adiponectin) play a central role in tumor initiation and progression by modulating cell proliferation, angiogenesis, inflammation, and the tumor microenvironment. Hormonal dysregulation—common in obesity, physical inactivity, and insulin resistance—favors tumor development, especially in breast, prostate, and colon cancers. The chapter also details how physical exercise acts as an endocrine and immunometabolic modulator by reducing levels of estrogen, insulin, IGF-1, and leptin, while increasing adiponectin and stimulating anti-inflammatory myokines. Exercise positively influences key signaling pathways such as AMPK, mTOR, PI3K/Akt, and NF- κB, promoting both direct and indirect antitumor effects. In models of breast, prostate, and colon cancer, regular exercise reduces aromatase expression in adipose tissue, improves insulin sensitivity, decreases tumor angiogenesis, and supports intestinal homeostasis. Finally, the text reinforces the importance of exercise in modern oncology, aligned with the Exercise is Medicine concept, emphasizing its applicability in cancer prevention, control, and rehabilitation, as well as its potential for therapeutic personalization based on hormonal and metabolic profiles.

Keywords: Hormones. Carcinogenesis. Physical Exercise. Tumor Microenvironment.

RESUMO
O capítulo apresenta uma síntese abrangente das interações entre hormônios, carcinogênese e exercício físico, abordando bases bioquímicas, moleculares e aplicações translacionais. Inicialmente, destaca-se que hormônios esteroides sexuais (estrogênio, testosterona), hormônios metabólicos (insulina, IGF-1) e adipocinas (leptina, adiponectina) desempenham papel central na iniciação e progressão tumoral, modulando proliferação celular, angiogênese, inflamação e microambiente tumoral. A desregulação hormonal — comum na obesidade, sedentarismo e resistência à insulina — favorece o desenvolvimento de tumores, especialmente mama, próstata e cólon. O capítulo também detalha como o exercício físico atua como modulador endócrino e imunometabólico, reduzindo níveis de estrogênio, insulina, IGF-1 e leptina, aumentando adiponectina e estimulando mioquinas anti-inflamatórias. O exercício interfere positivamente em vias como AMPK, mTOR, PI3K/Akt e NF-κB, promovendo efeitos antitumorais diretos e indiretos. Em modelos de câncer de mama, próstata e cólon, a prática regular reduz aromatase no tecido adiposo, melhora sensibilidade à insulina, diminui angiogênese tumoral e favorece a homeostase intestinal. Por fim, o texto reforça a importância do exercício na oncologia moderna, alinhado ao conceito de Exercise is Medicine, destacando sua aplicabilidade na prevenção, controle e reabilitação oncológica, além do potencial para personalização terapêutica baseada em perfis hormonais e metabólicos.

Palavras-chave: Hormônios. Carcinogênese. Exercício Físico. Microambiente Tumoral.

RESUMEN
El capítulo presenta una síntesis amplia de las interacciones entre hormonas, carcinogénesis y ejercicio físico, abordando bases bioquímicas, moleculares y aplicaciones traslacionales. Inicialmente, se destaca que las hormonas esteroides sexuales (estrógeno, testosterona), las hormonas metabólicas (insulina, IGF-1) y las adipocinas (leptina, adiponectina) desempeñan un papel central en la iniciación y progresión tumoral, modulando la

proliferación celular, la angiogénesis, la inflamación y el microambiente tumoral. La desregulación hormonal —común en la obesidad, el sedentarismo y la resistencia a la insulina— favorece el desarrollo de tumores, especialmente de mama, próstata y colon. El capítulo también detalla cómo el ejercicio físico actúa como modulador endócrino e inmunometabólico, reduciendo los niveles de estrógeno, insulina, IGF-1 y leptina, aumentando la adiponectina y estimulando mioquinas antiinflamatorias. El ejercicio interfiere positivamente en vías como AMPK, mTOR, PI3K/Akt y NF-κB, promoviendo efectos antitumorales directos e indirectos. En modelos de cáncer de mama, próstata y colon, la práctica regular reduce la aromatasa en el tejido adiposo, mejora la sensibilidad a la insulina, disminuye la angiogénesis tumoral y favorece la homeostasis intestinal. Finalmente, el texto refuerza la importancia del ejercicio en la oncología moderna, en línea con el concepto Exercise is Medicine, destacando su aplicabilidad en la prevención, control y rehabilitación oncológica, además del potencial para la personalización terapéutica basada en perfiles hormonales y metabólicos.

Palabras clave: Hormonas. Carcinogénesis. Ejercicio Físico. Microambiente Tumoral.

1 INTRODUCTION

Cancer is one of the main causes of morbidity and mortality in the world, being characterized by a set of diseases in which there is uncontrolled cell growth and proliferation, associated with the capacity for tissue invasion and metastasis (HANAHAN, 2022). Tumor development and progression are multifactorial processes, influenced by genetic, environmental, metabolic, and hormonal aspects. In this context, the functions of hormones, especially sexual and metabolic hormones, assume a central position, given their ability to directly modulate gene expression, intracellular signaling, and the tumor microenvironment (CALLE & KAAKS, 2004).

At the same time, evidence accumulated over the last decades indicates that physical exercise exerts a protective function in carcinogenesis and can act as an adjuvant therapy during cancer treatment. The effects of exercise on the endocrine system, energy metabolism and systemic inflammation point to a favorable hormonal modulation, capable of positively interfering with the pathways associated with oncogenesis and tumor progression (FRIEDENREICH & ORENSTEIN, 2002; CAMPBELL et al., 2025).

The integration between endocrinology, molecular oncology, and exercise physiology paves the way for a broader understanding of cancer biology and adaptive response to exercise. Thus, this chapter aims to discuss the biochemical and molecular bases of this interaction, addressing the main hormones involved in the carcinogenic process, the mechanisms by which physical exercise modulates these pathways, and the clinical and educational implications of this relationship in the context of health promotion and oncological rehabilitation.

2 HORMONES AND CANCER: BIOCHEMICAL AND MOLECULAR INTERACTIONS

2.1 SEX HORMONES AND HORMONE-DEPENDENT NEOPLASMS

Steroidal sex hormones, particularly estrogens and androgens, play critical roles in the development and progression of several types cancer, such as breast, endometrial and prostate. Estrogens exert their effects through binding to nuclear estrogen receptors (ERα and ERβ), modulating the transcription of genes related to cell proliferation, angiogenesis, and survival (THOMAS & GUSTAFSSON, 2011).

In postmenopausal women, most estrogens are synthesized by peripheral aromatization of androgens in adipose tissue, catalyzed by the enzyme aromatase (CYP19A1). Thus, the increase in fat mass is associated with an increase in estrogen production and, consequently, with a higher risk of breast cancer (CALLE & KAAKS, 2004; KEY et al., 2011). Elevation of serum estradiol levels and decrease of sex hormone-binding

globulin (SHBG) increase the free and biologically active fraction of the hormone, intensifying proliferative stimulation in sensitive tissues (Endogenous Hormones and Breast Cancer Collaborative Group, 2013). On the other hand, in men, high levels of testosterone and dihydrotestosterone (DHT) have been correlated with increased risk of prostate cancer, although the relationship is not linear, that is, there is no proportional relationship of the higher the level of testosterone or DHT, the greater the risk of prostate cancer, in a constant and predictable way. The action of these hormones occurs through binding to the androgen receptor (AR), a nuclear protein that, when activated, regulates genes that promote growth, proliferation, and differentiation of prostate cells. However, mutations or amplifications of this receptor can make it overactive, allowing tumor cells to continue proliferating even under conditions of low hormone concentration, which contributes to the emergence of resistance to androgen deprivation therapy, one of the main challenges in the treatment of prostate cancer (HEINLEIN & CHANG, 2004).

2.2 INSULIN/IGF-1 SYSTEM AND TUMOR METABOLISM

In addition to sex hormones, insulin-mediated signaling and insulin-like growth factor type 1 (IGF-1) represents one of the main hormonal axes related to carcinogenesis. Hyperinsulinemia, common in obese and sedentary individuals, stimulates tumor growth by multiple mechanisms: it increases the bioavailability of IGF-1 by suppressing binding proteins (IGFBPs), activates proliferative pathways such as PI3K/Akt/mTOR and Ras/Raf/MAPK, and inhibits cell apoptosis (POLLAK, 2008).

These signaling pathways are crucial for cell growth and survival, and are often dysregulated in tumors. Chronic activation of the PI3K/Akt pathway, for example, increases glucose uptake and stimulates lipid and protein synthesis, favoring the proliferative metabolic phenotype characteristic of cancer (WARD & THOMPSON, 2012). In this way, the endocrine and metabolic imbalance associated with insulin resistance develops an environment favorable to uncontrolled cell proliferation and tumor progression.

In addition, epidemiological studies reinforce this relationship, demonstrating that individuals with type 2 diabetes have a higher risk for several cancers, such as liver, colon, pancreatic and breast cancers (GIOVANNUCCI et al., 2010). In this context, glycemic control and improvement of insulin sensitivity are strategies of double importance, metabolic and oncoprotective, contributing not only to the regulation of energy metabolism, but also to the reduction of the risk of neoplastic transformation.

2.3 ADIPOKINES, INFLAMMATION AND TUMOR MICROENVIRONMENT

Adipose tissue, previously considered only as an energy reserve, is now recognized as an active endocrine organ. capable of secreting several bioactive molecules known as adipokines. Among them, leptin, adiponectin and resistin stand out, which exert systemic effects that influence carcinogenesis. Leptin, often elevated in obesity, acts in a pro-tumor manner, stimulating proliferation, angiogenesis and cell invasion, in addition to potentiating the mitogenic effects of estrogens, favoring the growth of malignant cells (JARDÉ et al., 2011).

On the other hand, adiponectin has the opposite effect by promoting insulin sensitivity, reduced inflammation, and inhibiting tumor growth through activation of the AMPK pathway, which antagonizes mTOR signaling, reducing the synthesis of proteins and lipids essential to tumor proliferation (WANG & SCHERER, 2016). Thus, the ratio between leptin and adiponectin is considered a relevant metabolic and hormonal marker in the assessment of risk for the development of cancer.

In addition, the chronic low-grade inflammation associated with obesity intensifies this pro-tumor environment. Inflammatory cytokines such as TNF-α, IL-6 and IL-1β stimulate the local production of reactive oxygen species (ROS), favoring the genetic mutations and activating inflammatory signaling pathways, such as NF-κB and STAT3, that support cell survival and expansion (COUSSENS & WERB, 2002).

2.4 INTERACTION BETWEEN HORMONES AND TUMOR MICROENVIRONMENT

The tumor microenvironment (TME) is composed of a complex network of cells and structural components, including immune cells, tumor-associated fibroblasts (CAFs), endothelial cells, adipocytes, and extracellular matrix. This dynamic ensemble constantly interacts with neoplastic cells, influencing their proliferation, invasion, and metastatic capacity.

Hormones profoundly modulate this ecosystem, directly affecting cellular communication and tumor behavior. Estradiol, for example, can regulate the expression of VEGF, promoting angiogenesis, and, consequently, the increase in tumor vascularization, which favors the growth and dissemination of malignant cells (ARNAL et al., 2017).

Similarly, IGF-1, secreted by fibroblasts and adipocytes in TME, stimulates the survival of neoplastic cells and contributes to resistance to hormonal therapies, such as aromatase inhibitors (POLLAK, 2012).

These evidences reinforce that hormonal actions are not limited to the isolated tumor cell, but extend to the modulation of the microenvironment that sustains, protects, and

promotes neoplastic progression, demonstrating the importance of the interaction between endocrine signaling and TME components in the evolution of cancer.

3 HORMONAL MECHANISMS INVOLVED IN CARCINOGENESIS

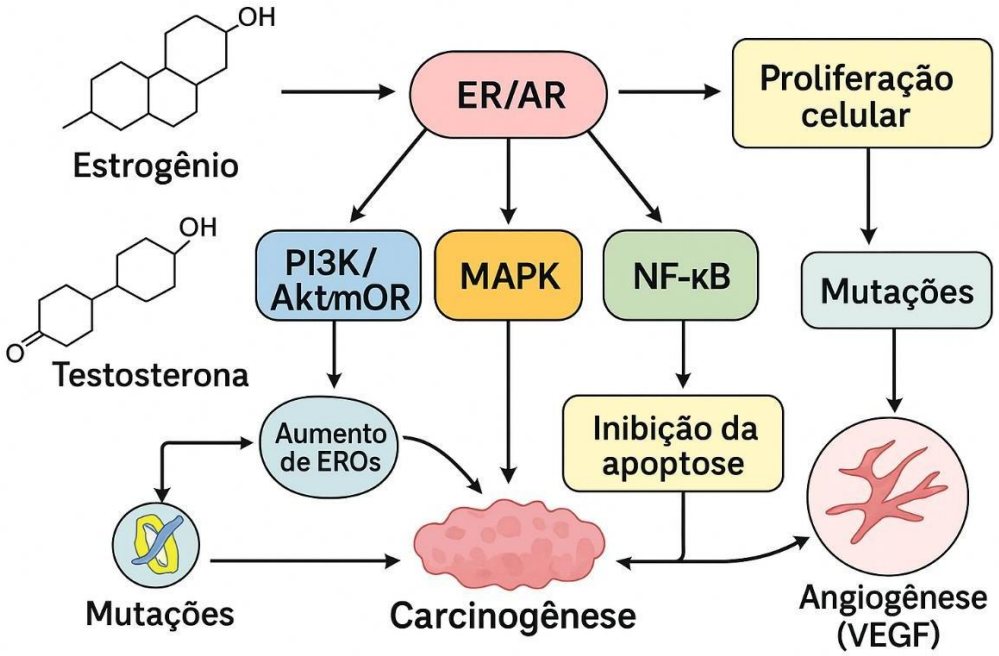
Hormones play essential roles in regulating tissue homeostasis, cell growth, and differentiation. However, in pathological contexts, they can act as tumor promoters, stimulating the proliferation of cells with pre-existing mutations or favoring inflammatory and angiogenic microenvironments that support tumor progression (HANAHAN; WEINBERG, 2011).

In the case of sex steroid hormones, such as estrogen and testosterone, a well-established relationship with breast, prostate, and endometrial cancer stands out. Estrogen, by binding to the nuclear receptors ERα and ERβ, regulates the transcription of genes involved in the cycle and cell survival (CLUSAN et al., 2023). In cells with mutations in the BRCA1, PIK3CA, and TP53 genes, this activation can result in uncontrolled proliferation and resistance to apoptosis (CLUSAN et al., 2023). On the other hand, testosterone and its metabolites, such as dihydrotestosterone (DHT), activate the androgen receptor (AR), modulating pathways such as MAPK and PI3K/Akt, often hyperactivated in prostatic neoplasms (CHEN et al., 2021). The overexpression of RA or mutations that alter its hormonal sensitivity are critical factors in the transition from prostate cancer to the castration-resistant state (WANG et al., 2020).

In addition to sex steroids, metabolic hormones such as insulin and IGF-1 (insulin-like growth factor) exert a significant influence on carcinogenesis. The insulin/IGF-1 axis activates the PI3K/Akt/mTOR pathway, promoting proliferation and inhibiting apoptosis (POLLOCK et al., 2021). This pathway is especially relevant in individuals with metabolic syndrome, obesity, and insulin resistance, conditions known to be associated with increased risk of breast, liver, and pancreatic cancer (GARCIA et al., 2022). Figure 1 presents a detailed cell diagram showing how estrogen and testosterone bind to their receptors (ER/AR), activating pathways such as PI3K/Akt/mTOR, MAPK and NF-κB, resulting in cell proliferation and inhibition of apoptosis.

Figure 1

Major signaling pathways stimulated by steroid hormones in carcinogenesis



Source: Adapted from Hanahan and Weinberg (2011) and Chen et al. (2021). Note: PI3K: Phosphatidylinositol-3-kinase; Akt: Protein kinase B; mTOR: Target of rapamycin in mammals; MAPK: Mitogen-activated protein kinase; NF-κB: Nuclear factor kappa B; ER/AR: Estrogen and androgen receptors; ROS: Reactive Oxygen Species; VEGF: Vascular endothelial growth factor.

At the molecular level, the chronicity of hormonal exposure and continuous signaling result in increased production of reactive oxygen species (ROS), DNA mutations, and genomic instability. This oxidative and inflammatory imbalance creates an environment conducive to neoplastic transformation (KARANTZA, 2011).

4 EFFECTS OF PHYSICAL EXERCISE ON THE HORMONAL AND TUMOR ENVIRONMENT

Physical exercise acts as a systemic modulator of hormones, cytokines, and metabolites, directly and indirectly influencing the tumor environment. During and after physical exercise, myokines are released, which are proteins produced and secreted by skeletal muscle fibers in response to muscle contraction. These substances, such as interleukin-6 (IL-6), IL-10 and irisin, which exert an anti-inflammatory function and regulate insulin sensitivity (PEDERSEN; FEBBRAIO, 2012).

In addition, exercise reduces circulating levels of insulin and IGF-1, decreasing proliferative stimulus on tumor cells dependent on these pathways (DIELI-CONWRIGHT; SLATTERY, 2019). In women with breast cancer, regular aerobic and resistance training programs showed a significant reduction in serum estrogen and leptin concentration, with an

increase in adiponectin, a hormone with an antiproliferative and anti-inflammatory effect (FRIEDENREICH et al., 2020).

In animal models, exercise was able to reduce the expression of VEGF and HIF-1α, modulating tumor angiogenesis and promoting better tissue oxygenation (KASUYA et al., 2022). This adaptation contributes to lower hypoxia and, consequently, lower activation of pro-tumor pathways associated with anaerobic metabolism (KASUYA et al., 2022).

From an immunological point of view, regular physical exercise increases immune surveillance, stimulating the activity of NK (natural killers) and cytotoxic T lymphocytes (SCHEDIN; HANKINSON, 2020). This response is partially mediated by catecholamines and by the modulation of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in a more balanced and physiological cortisol secretion, which favors the Inflammation control and anti-tumor immune response (SCHEDIN; HANKINSON, 2020).

5 SIGNALING PATHWAYS AND MOLECULAR MODULATION BY EXERCISE

Physical exercise modulates multiple intracellular signaling pathways that directly influence cellular energy metabolism, gene expression and tumor cell behavior. Among the main ones, the AMPK, mTOR, PI3K/Akt, NF-κB, and p53 pathways stand out, all of which are strongly associated with the regulation of cell growth and survival.

During physical activity, AMPK activation occurs, which leads to the inhibition of mTORC1, reducing protein synthesis and disordered cell growth (HARDIE, 2014). This modulation exerts an antagonistic effect on IGF-1 and insulin-induced signaling, creating an intracellular environment less favorable to tumor proliferation (LEE et al., 2020).

The p53 protein, known as the "guardian of the genome", has its expression increased after regular exercise, facilitating DNA repair and inducing apoptosis in damaged cells (LIU et al., 2021). In parallel, physical exercise also reduces the expression of pro-inflammatory genes via inhibition of NF-κB, resulting in lower secretion of cytokines such as TNF-α and IL-1β, which are associated with chronic inflammation and tumor progression (GOMEZ-CABRERA et al., 2022).

These biochemical and molecular adaptations demonstrate that physical exercise can exert not only indirect antitumor effects (by reducing obesity and improving metabolic effects), but also direct, modulating the tumor microenvironment and cell biology acting on the pathways of cell survival, proliferation and death, which reinforces its potential as an adjuvant strategy in the prevention and control of cancer (HOTTENGA et al., 2023).

6 SPECIFIC EFFECTS: BREAST, PROSTATE, AND COLON CANCER

In breast cancer, physical exercise works by reducing the activity of the aromatase enzyme in adipose tissue. Aromatase is responsible for converting androgens (such as testosterone and androstenedione) into estrogens (estradiol and estrone). In postmenopausal women, this pathway becomes the main source of estrogen in the body, since the ovaries cease hormone production. Thus, the reduction in aromatase expression induced by physical exercise decreases the peripheral synthesis of estrogens, resulting in less proliferative stimulus on breast cells expressing estrogen receptors (ER+). This effect contributes to reducing the risk of tumor progression and recurrence, in addition to improving metabolic and systemic inflammatory balance (FRIEDENREICH et al., 2020).

In prostate cancer, exercise reduces serum IGF-1 levels and increases the expression of binding proteins (IGFBP-3), which limits the availability of free IGF-1 and reduces proliferative stimulus on prostate cells (NIELSEN et al., 2022). In addition, there is an improvement in endothelial function and a reduction in prostatic inflammation, which may contribute to the inhibition of tumor progression (NIELSEN et al., 2022).

In colon cancer, physical exercise plays a protective role by multiple physiological and metabolic mechanisms. Physical activity increases intestinal motility, which reduces fecal transit time and, consequently, reduces the time of mucosal exposure to carcinogens from diet or hepatic metabolism. In addition, exercise positively modulates the intestinal microbiota, favoring growth by stimulating beneficial bacterial species capable of producing butyrate, a short-chain fatty acid with anti-inflammatory, antioxidant, and antitumor properties. Butyrate works by inhibiting uncontrolled cell proliferation, inducing apoptosis in abnormal cells, and regulating the expression of genes related to cell differentiation and epithelial integrity. In this way, regular exercise contributes to intestinal homeostasis and to reducing the risk of developing colorectal cancer (ZHANG et al., 2021).

This evidence reinforces that physical exercise should be recognized as an essential component of oncological therapy, acting in an integrated manner with hormonal, metabolic and inflammatory control, in addition to contributing to the modulation of the tumor microenvironment and to the improvement of the response to treatment.

7 TRANSLATIONAL CONSIDERATIONS AND CLINICAL APPLICABILITY

The integration between molecular endocrinology and exercise physiology offers a promising field for personalized therapeutic interventions in oncology. The concept of "exercise as medicine" (Exercise is Medicine) proposes prescription based on mechanisms,

where the intensity, duration, and type of exercise are adjusted according to the patient's hormonal and metabolic profile (THORNTON et al., 2023).

Supervised exercise programs have shown not only improvement in the quality of life of cancer patients, but also reduction in markers of systemic inflammation and improvement in the response to chemotherapy (COURNEYA et al., 2018).

To optimize clinical benefits, exercise prescription should consider variables such as insulin resistance, body composition, nutritional status, and the functioning of the hypothalamic-pituitary-adrenal (HPA) axis, in order to enhance beneficial hormonal and metabolic modulation, minimizing the risk of fatigue, catabolism, or immunosuppression.

8 CONCLUSIONS

Hormones are a central link between metabolism, cell proliferation and carcinogenesis. Prolonged exposure to dysregulated hormonal environments, especially involving sex steroids and metabolic anabolic hormones, favors tumor initiation and progression.

Physical exercise, in turn, represents an intervention of high translational relevance, capable of modulating biochemical pathways, reducing systemic inflammation, balancing the hormonal profile, and restoring cellular homeostasis. Understanding these molecular interactions is essential for the development of integrated and personalized therapeutic strategies, in which exercise acts not only as an adjuvant tool, but as a regulatory agent of tumor biology.

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