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THE IMMUNOMODULATORY EFFECT OF ENDURANCE EXERCISE (EE) AND RESISTANCE EXERCISE (RE) ON HEALTHY AND CANCER SUBJECT THROUGH THE KYNURENINE PATHWAY

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ABSTRACT

The kynurenine pathway breaks down tryptophan, an amino acid found in many foods, producing kynurenine that affects the immune system. Acute and resistance exercise modify this pathway, enhancing immune function by influencing immune cell mediators. This literature review explores the effects of exercise on the kynurenine pathway and immune system, summarizing ten clinical trials. Findings indicate that exercise impacts the pathway and immune system. Three studies show that acute and chronic endurance training increases kyn clearance and reduces kynurenine levels in healthy individuals. Two studies demonstrate that cancer patients can modify their immune systems by decreasing kynurenine levels and adjusting the kynurenine-tryptophan ratio. However, one study shows no impact on kynurenine levels in depressed patients undergoing endurance and strength training. Another study observed increased kynurenine levels and the kynurenine-tryptophan ratio. Additionally, a study reveals that both endurance and resistance exercise elevate CD3+ lymphocyte expression and PD-1+ CD8+ T-cells in the short term. By modulating immune cell mediators, exercise influences the kynurenine pathway, improving immune function. Exercise therapies can decrease kynurenine and increase tryptophan and kynurenic acid in cancer patients, enhancing immune function and reducing inflammation. This research suggests that exercise serves as a non-pharmacological intervention to prevent chronic diseases associated with inflammation and immune dysfunction.

Keywords: exercise; adult; healthy; cancer; kynurenine; immunomodulatory; innate immune system; adaptive immune system

INTRODUCTION

As of 2020, slightly more than 1 billion individuals are 60 or older, accounting for 13.5% of the world's total population of 7.8 billion. Since 1980, when the figure was only 382 million, it has climbed 2.5 times. The number of elderly people is expected to reach about 2.1 billion by the year 2050.(1) The aging population has contributed to an increase in the prevalence of age-related infectious illnesses and cancer, which can be traced in part to the natural reduction in immune system function known as "immunosenescence." Immunosenescence is a syndrome in which the immune system deteriorates as a

result of age, causing alterations in both innate and adaptive immunity. This degradation impacts immune cell function and features, including the expression and activity of immune cell receptors, resulting in a loss of immunological function such as chemotaxis and intracellular death. These alterations, in turn, weaken the body's response to pathogens, raising the risk of age-related disorders like cardiovascular disease, Alzheimer's disease, and diabetes. Furthermore, an aging immune system creates a pro-inflammatory milieu, which raises the likelihood of persistent infections and autoimmune illnesses, ultimately contributing to biological aging.(2)

Immunosenescence, also known as immunopause, is a complex aging phenomena involving numerous variables and biological events. These events include a decrease in both humoral and cellular immunity, an increase in the background of inflammation and oxidation, known as inflammaging and oxi-inflammaging, and the generation and release of auto-antibodies, which can contribute to the development of autoimmune illnesses.(3) Increasing exercise, according to some studies, may be an effective method for reducing chronic inflammation in older people.(4)

The kynurenine pathway, which yields multiple physiologically active chemicals, is the principal route by which tryptophan is broken down. While protein synthesis and serotonin/melatonin production only require trace amounts of tryptophan, the kynurenine pathway catabolizes more than 90% of the important amino acid.(5)(6) The first bioactive metabolite produced along this pathway is kynurenine (Kyn), and subsequent metabolites have shown the ability to affect both the immunological and central neurological systems.(7)(8) Certain gut bacteria have the ability to alter the host's serotonin production in enterochromaffin cells, and some can transfer serotonin to the host, potentially boosting inflammation and influencing neutrophil activity. (9)

Acute and chronic exercise both impact the regulation of the KYN pathway. Human evidence on the effects of chronic exercise on the KYN pathway, on the other hand, is conflicting, with many studies revealing no significant impact on circulating metabolites due to low training frequency intensity ratio or a lack of information on exercise modalities and adherence.(10)

In healthy individuals, the kynurenine pathway involves enzymes called tryptophan 2,3-dioxygenase (TDO) and indoleamine 2,3-dioxygenase (IDO) 1 and 2. TDO is mainly found in the liver and is stimulated by tryptophan or glucocorticoids. On the other hand, IDO can be found in various human cells. IDO1 and IDO2 have different expression levels, effects on metabolites, and enzyme activity based on specific physiological conditions. The role of IDO2 is not well understood yet. IDO activity is closely linked to the immune system, and peripheral blood mononuclear cells (PBMCs) are known to produce IDO. Under normal conditions, TDO is responsible for most of the conversion of tryptophan to kynurenine (KYN) for immune homeostasis. However, inflammatory stimuli cause a significant increase in IDO1-mediated conversion, especially when levels of interferon-gamma (IFN-y) and other pro-inflammatory cytokines like interleukin-6 (IL-6) and tumor necrosis factor (TNF)-α are elevated. KYN itself has immunomodulatory effects, including suppression of cytotoxic T-cell and NK-cell activity, as well as the differentiation of regulatory T-cells (Tregs). The IDO1-mediated conversion to KYN activates the aryl hydrocarbon receptor (AHR), which plays a role in T-cell differentiation. Chronic inflammation leads to a decrease in available tryptophan, which is essential for serotonin synthesis, resulting in impaired serotonin production. (11)

Whereas the kynurenine pathway in cancer influenced by factors like cortisol levels and inflammation, and it plays a role in immune function, energy metabolism, and inflammation regulation. "Immune privilege" refers to the inhibition of inflammatory reactions. The kynurenine pathway is involved in maintaining immune privilege by regulating local and systemic responses to reduce inflammation. This pathway is also important in immune escape in cancer. The pathway generates tolerance in immune-privileged sites and tumor microenvironments. It plays a role in generating regulatory T cells (Tregs) and can be triggered by tumor cell cytokines and chemokines. The four main mechanisms of the kynurenine pathway in regulating the immune response are tryptophan depletion, activation of the aryl hydrocarbon receptor (AhR), induction of Tregs, and blocking IL-2 through kynurenine. Other factors implicated in immunological tolerance include PD-1/PD-L1 expression in tumor cells and macrophage MIF expression.(12)

The kynurenine pathway has been linked to various chronic diseases and may serve as a therapeutic target. Exercise, especially endurance and resistance training, can modulate the kynurenine pathway and influence immune function by affecting the production and clearance of kynurenine metabolites. However, further research is needed to fully understand the effects of exercise on the kynurenine pathway and its implications for health and disease.After discovering that skeletal muscle is primarily responsible for the exercise-induced increase in KynA.(13) Researchers conducted further studies to investigate whether KynA has the potential to act as a myokine. These investigations found that increasing KynA to post-exercise levels in mice on a daily basis for 1 to 4 weeks resulted in weight loss due to decreased adiposity. When mice were given KynA, the immune cell makeup in adipose tissue changed, resulting in a shift to a more anti-inflammatory phenotype. These effects were mediated by GPR35 signaling (described further below) and subsequent PGC-1 overexpression. GPR35 mutant mice were not responsive to KynA- or exercise-induced browning of adipose tissue, confirming KynA's role as an exercise-induced myokine that influences systemic energy expenditure and immune system regulation. Other KPM receptors are present in diverse peripheral organs, indicating that other KPMs may also act as myokines. (14)(15)

The period of sample collection should be carefully examined when assessing the effects of acute or chronic exercise on the KYN pathway. Acute exercise samples should be collected shortly after activity and throughout recovery to show result kinetics, whereas chronic exercise samples should be collected in a resting state, usually 24 hours or longer after the last exercise session. Incomplete recovery and adaption mechanisms following acute exercise, on the other hand, could potentially skew the outcomes of chronic exercise, resulting in no apparent effects.(16)(17)

This review summarizes known research on the effects of KP on immunological regulation. Following a brief description of the pathway's metabolites and enzymes, we summarize findings that suggest linkages between KP and immune function in exercised cancer and healthy subjects.

METHODS

The search process involved using electronic databases such as Web of NCBI PubMed to identify published journal articles that explored the role of emotions in eating disorders (EDs). The search was limited to articles published between 2013 and 2022, and it was updated in March 2023. The search terms used were based on three categories: kynurenine, exercise, immune, endurance exercise, resistance exercise, health cancer,and adult. These categories were combined using "OR" and "AND" operators, and truncation was applied to key terms. Additionally, the reference lists of obtained full-text articles were examined for potentially relevant articles. The systematic literature search followed the PRISMA guidelines, as well as the guidelines from the Evidence for Policy and Practice Centre (EPPI-Centre, 2008).

RESULTS

Three studies show that exercise influences the kynurenine pathway and immunological function. Acute and continuous endurance training in healthy people resulted in reduced kynurenin levels and increased kynurenine clearance. (18)(19) Patients with cancer can modify their immune systems by lowering kyn levels and lowering the kyn/trp ratio with acute and chronic resistance exercise.(20)(21) Meanwhile, Millischer found no difference in kyn levels in depression patients who received acute and chronic endurance and strength training. While on older healthy women who underwent acute endurance activity, kyn levels and the kynurenine tryptophan ratio increased. Furthermore, one study concentrated on the acute effects of endurance and resistance exercise on the immune system without particularly assessing kynurenine pathway metabolites. It was discovered, however, that both types of exercise boosted the expression of CD3+ lymphocytes after both EE and RE, as well as an increase in PD-1+ CD8+ T-cells after EE. Only after EE did the proportions of T-cell populations change.(22)

Table 1. Endurance exercise (EE) and resistance exercise (RE) related to kynurenine and immune system

No.	Reference	Method	Type of Exercise	Effect to Kynurenine Pathway	Effect on immune cell
1	Joisten et. al (2020) (22)	Healthy male adults completed both a resistance exercise (RE) and an acute endurance exercise (EE) session. Blood samples were obtained before, shortly after, and one hour after the completion of each exercise session. Estimated ratios and serum concentrations of TRP, KYN, kynurenic acid (KA), and quinolinic acid (QA) were among the results. The gene expression of indoleamine 2,3 dioxygenase (IDO) 1 and kynurenine aminotransferase (KAT) 4 was examined in this work. PBMCs are also known as peripheral blood mononuclear cells. Cortisol and Interleukin (IL)-6 serum concentrations were also examined, as these are two potential KYN pathway mediators. This study looked at the early correlations between immune cell types, potential mediators, and results of the KYN pathway's initial activation.	Endurance exercise (EE) and resistance exercise (RE).	There was a substantial time effect on KYN/TRP ratio in RE EE following exercise, there was an increase in KA and KA/KYN ratio, followed by a reduction in the follow-up measurement. KAT4 expression increased following EE exercise, and QA levels were higher after the EE session.	The ratio of KYN to TRP IL-6 (+) CD56 (+) NK-cells, (+) cytotoxic T-cells (-) CD56dim (-) NK cells. (-)
2	Saran et.al (2021) (19)	The study involved 35 Caucasian adults (25 women and 10 men) who were not frequent exercisers. The	bicycle cycloergometer (Endurance Exercise)	The presence of kynurenine aminotransferase (KAT) activity in sweat samples.	Not measured

	participants' mean age was 47.62 years (SD15.91), and their mean Body Mass Index (BMI) was 24.36 kg/m2 (SD3.29). Under medical supervision, the participants completed a four-week daily exercise program, except on Saturdays and Sundays. The regimen included two periods of cycloergometer training, followed by elliptical cross-trainer movements. Training on each device was gradually increased over four weeks, from eight minutes in the first week to 15 minutes in the third and fourth weeks, with no breaks longer than 30 seconds between exercises. The exercise intensity was low, and the activities were carried out in an air-conditioned gymnasium at a temperature of 23-24°C. Sweat samples were obtained on days one, fourteen, and twenty-eight of the training using two separate ways to account for potential mistakes due to sweat collecting method specificity. Method A involves applying a commercial absorbent patch (Pharm	Indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO) activity was considerably decreased.

		Chem Inc., USA) between the shoulder blades before beginning the training session and removing it immediately after finishing the daily workout. Method B entailed taking a sweat sample (a drop of perspiration) from the patient's forehead with a cotton wool swab immediately after the daily training was completed.			
3	Zimmer et. al (2019)(23)	A study comprised 96 breast cancer patients who had not received chemotherapy. They were randomly allocated to one of two groups: exercise/intervention (IG) or control (CG). For 12 weeks, the IG followed a supervised progressive resistance training program twice a week, while the CG followed a supervised relaxation program. TRP and KYN levels in the blood, as well as KYNA and neurotoxic QUINA levels in the urine, were measured before (t0), after radiation, at mid-term of the exercise intervention (t1), and after the exercise intervention (t2). 24 healthy women (HIG) also participated in the exercise program to examine potential differences in the	Resistance Exercise (RE)	Serum KYN levels were significantly lower and the KYN/TRP ratio was lower in exercisers than in non-exercisers (CG).	Not measured

		impact on KYN metabolites between breast cancer patients and healthy individuals.			
4	Pal et.al (2020) (24)	Following a cardiopulmonary exercise test (CPET), 21 adult patients with breast and prostate cancer were randomly randomized to 12-week intervention programs of endurance standard training or endurance polarized training. Serum was taken before CPET, immediately after CPET, one hour after CPET, and 12 weeks after the intervention. Flow cytometry was used to look for AhR, IDO, KIR2DL1, and NKG2D in NK-92 cells that had been treated with autologous serum. For acute impacts, analysis of variance was employed, while for chronic effects, analysis of covariance was used.	Endurance Exercise (EE)	Chronic and acute EE have the capacity to suppress the AhR/IDO axis.	Chronic and acute EE activate NK cells cytotoxicity.
5	Pal et. al (2020) (20)	The trial comprised 65 adult pancreatic cancer patients shortly after resection, and the intervention phase lasted 6 months, beginning 12 weeks after surgery with resistance training twice a week. Except for one patient who did not have surgery, the baseline (t0) was acquired at this point, and training began	Resistance Exercise (RE)	Reduce kynurenine/tryptophan levels (indicative of IDO/TDO enzyme), hence regulating the immune system	IL-6 levels decreased over the first three months for both intervention groups.

		immediately following randomization.			
6	Schenk et. al (2020)(21)	In this study, 24 healthy males (age: 24.63.9 years; weight: 83.910.5 kg; height: 182.46.2 cm) did a single bout of both resistance and endurance exercise on consecutive days in a randomly assigned order. Blood was drawn before (t0), after (t1), and one hour after (t2) in both circumstances. Flow cytometry was used to assess T-cell populations, cytoplasmic AhR content, and surface PD-1.	Endurance exercise (EE) and resistance exercise (RE) session.		RE & EE: increase in CD3+ decreased cytoplasmic AhR Decrease PD-1+ EE: increase in CD8+ T-cells T-cell .
8	Strasser et. al (2016)(18)	This study included 33 healthy and trained athletes who met certain requirements such as having no history of muscle condition, cardiac or kidney disease, not taking any medication, and not drinking alcohol on a regular basis. Each participant completed a questionnaire detailing their medical history and prior training. In this study, the eligible people (17 women and 16 men) had endurance training, which included continuous endurance training at moderate intensity (60% to 80% peak oxygen consumption) done each week in the month before the test.	"Light exercise" (yoga-like classes), "moderate exercise" (intermediate-level aerobics class), and "vigorous exercise" (high-intensity aerobics/strength training) are the three levels of exercise.	Tryptophan concentrations were reduced while kynurenine levels increased	Neopterin concentrations increased considerably after exercise, indicating immunological activation. IFN-y participation is supported. Furthermore, exercise boosted macrophage IDO1 activity.

		Two hours before the exercise test, the participants were given a standardized breakfast that included an incremental cycle ergometer exercise.			
10	Joinsten et.al (2020) (21)	The study comprised 12 healthy individuals aged 19 to 32 who frequently engaged in strength training. To establish good movement control and a homogeneous sample, participants were asked to undertake at least one strength training session per week for the previous 6 months. The researchers took blood samples from individuals three times: before (T0), immediately after (T1), and one hour after (T2) completing two different types of loadings (HYP and MAX) in a randomized cross-over design. The serum concentrations of tryptophan (TRP), KYN, kynurenic acid (KA), and quinolinic acid (QA) were determined using high-performance liquid chromatography.	Resistance Exercise (RE)	According to the findings, acute HYP exercise, but not MAX exercise, temporarily increases the flow of the KYN route towards KA. This may result in peripheral KYN elimination and immunomodulatory effects.	Not measured

DISCUSSION

Exercise has been shown to benefit the immune system by improving immunological function and decreasing inflammation. Exercise has also been linked to changes in the kynurenine pathway. The

examined literature sheds light on the effects of acute and chronic exercise on kynurenine (kyn) levels and clearance in healthy individuals as well as cancer and depressed patients. In healthy people, acute and chronic endurance and resistance training were observed to promote kyn clearance and decrease kyn levels (Schenk and Joinsten). These were also discovered in healthy patients who performed acute endurance training, which was related with a fall in trp levels and an increase in kyn levels, implying an increase in trp catabolism (strasser, saran). Patients with cancer who received chronic resistance training had lower kyn levels and a lower kyn/trp ratio (Pal, Zimmer), indicating that resistance training may be an effective strategy to modify the immune system in cancer patients. This is consistent with previous research findings. Overexpression of IDO1 is related with poor patient survival in cancer patients, and phase III clinical trials using the IDO1 inhibitor Epacadostat indicate promising outcomes.(9)

Oncological research indicates one possible explanation for the link between exercise and anti-inflammatory benefits. According to research, tumor cells have higher activation of the kynurenine (KYN) pathway, which degrades tryptophan (TRP). Inflammatory signaling activates indoleamine-2,3-dioxygenase 1 (IDO1), the first enzyme in the KYN pathway, which converts TRP to KYN. KYN modulates the immune system and promotes Treg differentiation.Acute exercise has been shown in studies to robustly activate the KYN pathway, which may contribute to its anti-inflammatory effects in the short term. (25) The first activation of the KYN pathway following acute exercise is most likely caused by immunological activation caused by an increase in inflammatory cytokines such as IL-6. The activation of IDO1, IDO2, and KMO by IFN- and other inflammatory cytokines such as IL-6 significantly relates to the upregulation of the KYN pathway via IDO, resulting in enhanced breakdown of KYN to QA during acute exercise. Exercise's effect on nitric oxide and its possible function in suppressing IDO activity, resulting in persistent downregulation of the KYN pathway.(26)

Aside from suppressing IDO activity, the increase in metabolic flux towards KA following acute and chronic exercise may be connected to KAT expression in various tissues or cell types. Although the degradation of KYN to KA has primarily been examined in the setting of chronic exercise.(27) PGC-1 coactivator-mediated increases in KAT expression in skeletal muscle were accompanied by a decrease in KYN in blood plasma, according to the findings. PGC-1 has been shown to increase in skeletal muscle following both single bouts of aerobic exercise and continuous exercise training. It could account for the observed abrupt increase in metabolic flow towards KA. PGC-1 relies on DNA-binding transcription factors known as the peroxisome proliferator-activated receptor (PPAR) family as a transcriptional coactivator. In skeletal muscle, PPAR- and PPAR- are tightly connected with PGC-11, whereas PPAR- is mostly expressed in immune cells and modulates certain immune response pathways. Because PPAR expression is ligand-dependent and some of these ligands can be generated by exercise stimuli, the PPAR family may play a crucial role in PGC-11-mediated KAT expression in response to acute exercise in skeletal muscle as well as other tissues. Although only peripheral mononuclear immune cells showed enhanced KAT enzyme expression after acute exercise, more study into KAT enzyme expression in skeletal muscle is needed. Acute resistance exercise may also be associated to the PGC-14 isoform, which has been linked to skeletal muscle hypertrophy regulation and resistance training. Long-term anti-inflammatory effects of exercise can be achieved in two ways. For starters, it can reduce the amount of visceral fat, which is a major source of inflammation. Second, frequent exercise can improve the body's overall ability to resist inflammation.(28)

Skeletal muscle, which is an important part of the locomotor system and accounts for a large fraction of lean body mass (up to 40%), is important for glucose uptake after meals and for maintaining body temperature. (30)It also provides amino acids, which are utilized by several organs during critical conditions.Exercise can change the composition and function of skeletal muscle, resulting in a variety of health advantages that go beyond energy homeostasis. Skeletal muscle is becoming recognized as an endocrine organ that produces myokines, which can affect metabolism, inflammation, and cell proliferation in a variety of ways.(28)

Large neutral amino acid transporters (LATs) in muscle fibers carry Kyn and Trp, competing with other amino acids. (34) LAT inhibition has been demonstrated to lower Kyn and KynA concentrations in the muscles. In skeletal muscles, LAT1 and LAT2 form heterodimer complexes with CD98, with type 2

fibers carrying more LAT1 than type 1 fibers.(29) LAT1 and CD98 expression rises in response to acute resistance exercise in both young and old persons.(22) Some KPMs, such as 3-HK in striatal neurons and KynA and XA in cells, can be imported into cells via organic anion transporters 1 and 3 (OAT1/SLC22A6 and OAT3/SLC22A8), which have been immunohistochemically detected in human muscle fibers. However, because KynA and XA have lower plasma concentrations than Kyn and Trp, and LATs are blocked competitively by other amino acids, the majority of KPMs are likely generated within the muscle.(39)(40) Many kynurenine pathway enzymes are found in muscle fibers, including kynurenine aminotransferases (KATs), kynureninase (KynU), kynurenine 3-monooxygenase (KMO), and 3-hydroxyanthranilate 3,4-dioxygenase (3-HAO). Because skeletal muscle has low IDO expression and TDO activity, kynurenine (Kyn) is more likely generated in the liver or immune cells and delivered into muscle fibers. Kyn can be converted into KynA, AA, or 3-HK once inside the muscle fiber. The PGC-11/PPAR/ signaling pathway increases the production of KATs, which convert Kyn to KynA.(41) Pyridoxal-5′-phosphate (PLP), the active form of vitamin B6, is required by KATs to transfer an amino group from one substrate to another, resulting in kynurenic acid (KynA) from Kyn. KATs are highly flexible enzymes that have been classified into four types: KAT 1 (glutamine transaminase K and cysteine conjugate-lyase), KAT 2 (aminoadipate aminotransferase), KAT 3 (CCBL2), and KAT 4 (glutamic-oxaloacetic transaminase 2 and mitochondrial aspartate aminotransferase). From 3-hydroxykynurenine (3-HK), KATs can also create xanthurenic acid (XA). KATs employ Kyn and 3-HK to create KynA and XA in resting mouse skeletal muscle. KAT expression in muscle is regulated by PGC-11 and begins in oxidative fibers with high amounts of this coactivator. Exercise enhances the expression of KATs in skeletal muscle, according to studies on mice and humans.(22)

There have been few reports of transporters that carry metabolites from the Kynurenine pathway (KPMs) into cells. LATs, as well as OAT1/SLC22A6 and OAT3/SLC22A8, have been connected to the uptake of specific KPMs in neurons and muscle fibers.(45) However, because KynA and XA are found in low concentrations in the blood and because amino acids inhibit LATs, it is likely that the majority of KPMs are generated within muscle fibers.(35) (39) Although it is unknown how exercise changes Trp metabolite concentrations, KynA routinely increases following acute endurance exercise, and chronic endurance exercise in humans enhances the expression of all four KATs.(46) Chronic endurance exercise or PGC-1 overexpression in mice increases the expression of KAT 1, 3, 4, and 3-HAO but not KynU or KMO. In mice, a muscle-specific genetic deletion of PGC-1 suppresses both exercise-induced KAT expression and increased plasma KynA. It is currently unknown how much Kyn, KynA, and other Trp-metabolites are present in skeletal muscle fibers after exercise.(47) Exercise may influence the kynurenine pathway by decreasing the enzymatic activity of KMO and 3-HAO due to increased O2 consumption, as well as by suppressing PHDs, which use -ketoglutarate to hydroxylate HIF-1, making it available to KATs. This process has been proposed to explain how liver KATs manufacture KynA from skeletal muscle -ketoglutarate excess. These occurrences drive Kyn down the KynA and XA degradation branch via the NAD+ pathway. During submaximal activity, PLP is diverted to skeletal muscle, where it may fuel enzymes such as KATs and KynU that require this cofactor. Exercise can boost the production of KATs, which convert Kyn to KynA, while decreasing the activity of some enzymes involved in KPM metabolism, such as KMO and 3-HAO. Exercise may also transfer the cofactor PLP to skeletal muscle, where it can fuel enzymes like KATs and KynU that require this cofactor. However, the precise effects of exercise on the amounts of various Trp metabolites within muscle fibers remain unknown.(48)

GPR35 is a membrane protein that was found in 1997. It is typically related with Gi/o proteins, but when activated, it can also be coupled with other proteins such as G13, Gq/11, and -arrestin. GPR35 is mostly expressed in the gastrointestinal system and particular immune cells, although it is also found in neurons, parts of the central nervous system, vascular smooth muscle cells, endothelial cells, and adipocytes.(28) Because GPR35 was previously thought to be an orphan receptor, the identification of KynA as an endogenous ligand for it was noteworthy. Other compounds that have been found as possible GPR35 ligands include NPPB, Zaprinast, lysophosphatidic acid, and pamoic acid.(30) GPR35 activation has been linked to a variety of biological outcomes, including pain modulation, blood pressure regulation, immune response attenuation, and adipocyte energy expenditure. GPR35 expression is highest in human

immune cells such neutrophils, T cells, and dendritic cells and lowest in B cells, eosinophils, basophils, and platelets. The potential role of KynA and GPR35 in muscle-to-immune cell communication during exercise is being investigated. (29)The period of sample collection should be carefully examined when assessing the effects of acute or chronic exercise on the KYN pathway. Acute exercise samples should be collected shortly after activity and throughout recovery to show result kinetics, whereas chronic exercise samples should be collected in a resting state, usually 24 hours or longer after the last exercise session. (31)Incomplete recovery and adaption mechanisms following acute exercise, on the other hand, could potentially skew the outcomes of chronic exercise, resulting in no apparent effects.(29)

In healthy subject IDO activity closely interacts with the immune system. Especially peripheral blood mononuclear cells (PBMCs) have been shown to be potent producers of IDO.(32)(33) Based on immune homeostasis, IDO mediated conversion of TRP to KYN is suspected to be constant and almost entirely mediated by TDO under basal conditions. In contrast, local and systemic inflammatory stimuli provoke a dramatic increase in IDO1 mediated conversion.(34) Particularly, elevated levels of interferon-gamma (IFN-y)(35), but also increases in other pro-inflammatory cytokines, such as interleukin (IL)-6 (30) and tumor necrosis factor (TNF)-α (25), seem to be decisive stimuli for IDO induction. KYN itself possesses immunomodulatory effects comprising the suppression of cytotoxic T-cell, NK-cell activity (28) and mediating the differentiation of regulatory T-cells (Tregs).(16) Evidence suggests that the IDO1-mediated conversion to KYN activates the aryl hydrocarbon receptor (AHR), which plays a key role in T-cell differentiation.(31) Furthermore, a chronic inflammation-induced activation of the A consistent decrease in the bioavailability of TRP that is essential for the neurotransmitter serotonin seems to be one causal factor. If chronic inflammatory conditions are present, the degradation of available TRP through the KYN pathway is pathologically increased, which consequently leads to an impaired synthesis of the neurotransmitter serotonin. (22)

The kynurenine pathway is a metabolic route involved in the breakdown of tryptophan, an amino acid found in many foods. There are two main enzymatic pathways in tryptophan breakdown: the serotonin pathway and the kynurenine pathway. The kynurenine pathway is regulated by enzymes such as tryptophan 2,3-dioxygenase and indoleamine 2,3-dioxygenase, and it is responsible for the majority of tryptophan breakdown. This pathway produces kynurenine, which can be further converted into either neuroprotective kynurenic acid or neurotoxic quinolinic acid. The kynurenine pathway is influenced by factors such as cortisol levels, inflammatory cytokines, and the presence of inflammation. It plays a role in immune function, energy metabolism, and the regulation of inflammation. (11)

The phrase "immune privilege" was first used to describe the inhibition of inflammatory reactions within anatomically protected organs such as the eyes, brain, placenta, and testes. Cellular and metabolic systems that orchestrate immune responses, on the other hand, govern inflammation inside these sites. Our present understanding of tolerogenic pathways includes hair follicles, the colon, and cancer in the notion of immunological privilege. Cells harboring the enzyme indoleamine-2,3-dioxygenase catabolize tryptophan to create kynurenine metabolites, which regulate local and systemic responses to reduce inflammation, hence maintaining immunological privilege. The kynurenine pathway (KP) is a signaling mechanism that develops and maintains immune-privileged areas while also contributing to cancer immune escape. The discovery of the underlying molecular drivers of the KP in immune-privileged areas and cancer is critical for the development of innovative therapeutics to treat autoimmunity and cancer, as well as to improve transplantation results.The kynurenine pathway's role in generating tolerance in immune-privileged locations, malignancies, and tumor microenvironments.The generation of kynurenine by tumor cell and APC IDO enzymatic activity leads to immunological tolerance in immune-privileged locations and in the tumor microenvironment. Kyn plays an important role in generating Treg cells, which can also be directly triggered by tumor cell cytokines and chemokines. Tumor cells' cytokines and chemokines can also encourage APCs to activate the KP, which leads to tumor formation. The four key KP mechanisms that regulate the immune response are as follows: (1) Trp depletion followed by GCN2 induction and mTOR1 inhibition; (2) activation of AhR by Kyn; (3) Treg induction via CTLA-4 and PTEN expression; and (4) Kyn-mediated IL-2 blockage. Other variables implicated in immunological tolerance include tumor cell PD-1/PD-L1 expression and macrophage MIF expression. Trp concentrations are represented by dotted

lines.(12) Since IDO1 is upregulated in tumor microenvironment,(22) it is not surprising that IDO1 has recently attracted extended attention as promising immunotherapeutic target in cancer research.(34)

In this review a study of elite athletes (healthy subject) found that the quantity and proportion of circulating regulatory T-cells (Treg), which produce anti-inflammatory cytokines like Interleukin 10 and TGF-ß, are positively associated with endurance ability. Athletes were shown to have higher levels of circulating Treg than non-athletes of the same age. The short-term inflammation that occurs after each exercise session is thought to promote a long-term adaptation in the body's anti-inflammatory response, but the exact process is unknown.(31) Acute endurance training increased kyn levels and the kynirenine triptophan ratio in healthy older women.(36)

Nonetheless, animal models and a randomized controlled study in breast cancer patients have shown promising results.(37) Acute exercise activates the KYN pathway, as seen by lower levels of TRP and higher levels of KYN in human serum or plasma. The majority of these research concentrated on high-intensity aerobic activity, such as progressive exercise tests to exhaustion.(11)(38)Acute exercise also increases metabolic flow towards KA, possibly due to increased KAT enzyme expression. Furthermore, after intense exercise, the primary branch of the KYN pathway leading to QA can be increased.(31)(37) whereas Joisten et al discovered that hypertrophy strength exercise (HYP) can increase the metabolic flow of the KYN route towards kynurenic acid (KA), potentially promoting KYN clearance and immunomodulatory effects. According to the findings, future research should focus on the effects of strength training on the KYN pathway, particularly hypertrophic strength exercise modalities. These findings have substantial implications for a variety of clinical populations suffering from inflammatory disorders, as strength exercise-induced KYN pathway regulation may activate anti-inflammatory and neuroprotective actions. Longer-term research are needed to look into potential chronic modulations of the KYN pathway caused by strength training.(22) Tsuji et al. examined the tryptophan and kynurenine pathway's function in the development of immune-related illnesses. They discovered that an imbalance between pro-inflammatory and anti-inflammatory pathways may play a role in the etiology of certain immune-related disorders. They also highlighted that the kynurenine pathway could be a suitable target for the development of novel immunotherapies.(30)

CONCLUSION

In summary, In healthy individuals, exercise, especially endurance training, has been found to increase the levels of regulatory T-cells (Tregs) that produce anti-inflammatory cytokines. This suggests that exercise promotes an adaptive anti-inflammatory response in the body. Acute endurance training has also been shown to increase kynurenine levels and the kynurenine to tryptophan ratio in older women. Animal models and studies in breast cancer patients have shown promising results in activating the kynurenine pathway through acute exercise. High-intensity aerobic activity and hypertrophy strength exercise have been found to influence the metabolic flow within the kynurenine pathway, leading to increased levels of kynurenic acid (KA) and potentially promoting immunomodulatory effects. Strength training may have implications for clinical populations with inflammatory disorders, as it can activate anti-inflammatory and neuroprotective actions through the regulation of the kynurenine pathway. Imbalance between pro-inflammatory and anti-inflammatory pathways in the tryptophan and kynurenine pathway may contribute to the development of immune-related disorders, making the kynurenine pathway a potential target for novel immunotherapies. Further research is needed to explore the chronic modulations of the kynurenine pathway caused by strength training.

Endurance and resistance exercise (EE and RE) can affect the kynurenine pathway and improve immune function through influencing immune cell mediators. Exercise therapies in cancer patients can result in a drop in kynurenine levels and a rise in tryptophan and kynurenic acid, all of which are related with enhanced immune function and lower inflammation. According to this study, exercise can be used as a non-pharmacological intervention to improve immune function and perhaps prevent chronic diseases related with inflammation and immunological dysfunction. Futher research is needed, however, to completely understand how exercise impacts the kynurenine pathway and immunological function.

Depending on the demographic and health condition of concern, the best type, intensity, and duration of exercise for modifying the kynurenine pathway and boosting immune function may change. As a result, more complete recommendations for exercise as a therapeutic intervention will necessitate additional research into the effects of exercise on immunological function and the kynurenine pathway in healthy and cancer subject.

CONFLICT OF INTEREST

No conflicts of interest are disclosed by the authors.

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