NARRATIVE REVIEW

Irisin: A myokine with therapeutic and diagnostic potential in clinical dentistry

Alina Saleem, Sarah Ghafoor

Abstract

Irisin is a novel adipomyokine which has extensive systemic and local effects in different tissues of the body. The scientific interest in understanding the physiological roles of irisin in the body has increased tremendously in the past few years due to its vast therapeutic potential in different fields of medicine. The current narrative review was planned to describe the molecular mechanisms by which irisin regulates oral hard and soft tissues. The information gleaned provided useful insights for future researchers to investigate newly discovered roles of irisin in craniofacial health and disease, and to explore the potential of irisin as a promising therapeutic and diagnostic agent in clinical dentistry.

Keywords: FNDC5, Irisin, Human periodontal ligament cell, Human dental pulp stem cell, Bone, Regeneration.

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Introduction

Irisin is a polypeptide hormone predominantly released from skeletal muscles after exercise or exposure to cold. Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1-α) is a transcriptional coactivator that stimulates the expression of fibronectin type III domain-containing protein 5 (FNDC5) gene in muscles. The gene encodes FNDC5, which is a membrane protein in skeletal muscle cells that is cleaved at its C- terminal to produce irisin.[1] Irisin exerts systemic effects by travelling to various organs, like the brain and liver, and is involved in energy homeostasis and other important metabolic functions.[2] Since its discovery, numerous studies have reported the effects and actions of irisin in diverse tissues, but the role of irisin in oral tissues and oral homeostasis is still being investigated.[3-5] Recent advances have been made to understand the local effect of irisin in different tissues of the oral cavity. Irisin acts as a regulator of cementoblast proliferation and mineralisation, and as a promoter of odontogenic differentiation and angiogenesis in dental pulp cells.[6] Irisin also plays a role in cell growth, migration and osteogenic behaviour of human periodontal ligament (PDL) cells.[7] Raised levels of irisin are seen in the saliva of patients with oral inflammatory diseases, such as recurrent apthous stomatitis (RAS) and chronic periodontitis, which show that irisin can act as a potential salivary biomarker for such conditions.[8]

The current narrative review was planned to provide insights on the effects of irisin in the regulation of oral and facial tissues and its role in the working of the fundamental cells of the oro-dental tissues, such as PDL cells, pulp cells, cementoblasts and osteoblasts.

Department of Oral Biology, University of Health Sciences, Lahore, Pakistan.
Correspondence: Sarah Ghafoor. e-mail: sarahghafoor@uhs.edu.pk
ORCID ID. 0000-0002-3521-5955

Methods and Results

The narrative review was conducted from May to October 2022, and comprised of literature search that was done on electronic databases, such as PubMed and Google Scholar, using the medical subject heading (MeSH) terms, such as irisin, chronic periodontitis, exercise, dental tissues, in various combinations with or without Boolean operators, like dental tissues and irisin, exercise and irisin, alveolar bone, regeneration.

The sample size was determined using universal sampling method. As a result of the literature search, 418 studies related to the subject were found. Studies from the last 10 years were included in the review. Out of 418 research papers, therefore, 28(6.7%) studies were selected for detailed analyses. This selection was based on the inclusion criteria according to which included research paper only in the English language with full-texts available and those that had investigated the role of irisin protein within dental and orofacial tissues. Based on the exclusion criteria, 18(4.3%) studies published in language other than English and 200(48%) reports, letters and abstracts whose full texts were not available were excluded.

Irisin distribution and mechanism of action in different body tissues

Irisin is a novel myokine as well as an adipokine. Irisin plays an important role in lipid metabolism, thermogenesis, metabolic and cardiovascular health as well as in carrying out important functions in the central nervous system (CNS).[9] Irisin increases myocardial cell metabolism, promotes cell differentiation. Irisin increases hippocampal neurogenesis and brain-derived neurotrophic factor (BDNF) expression.[10] It also plays a very important role in the muscle and bone crosstalk.[11] It has been recently found

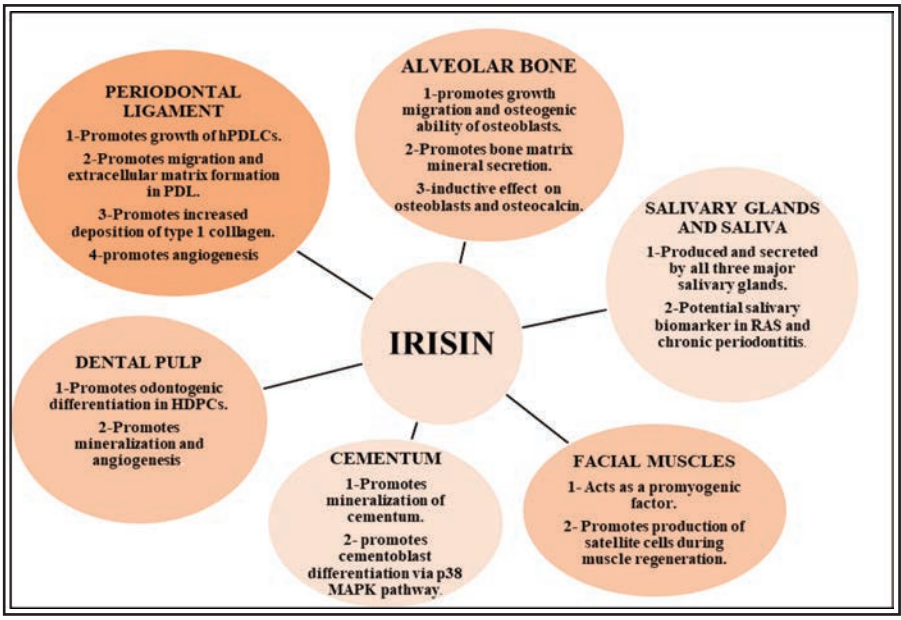

Figure-1: Summary of the effects of irisin in orofacial tissues.

PDLC: Periodontal ligament cells, RAS: Recurrent apthous stomatitis, HDPC: Human dental pulp cells, MAPK: Mitogen-activated protein kinase.

Table: Irisin in different tissues of the body.

Presence of irisin protein in different tissues of the body	
Skeletal muscles	Myocytes, connective tissue, epimysium, perimysium
Cardiovascular system	Myocytes, connective tissue, cardiac muscle, pericardium, vena cava
Nervous system	Brain, axon, myelin sheath, neurons, neuroglia, nerve cells, purkinje cells, intracranial artery, optic nerve, pituitary gland, spinal cord
Gastrointestinal system	Liver, pancreas, rectum, stomach, small intestine
Reproductive system	Testes, ovaries, leydig cells, oviduct, seminal vesicles, vagina
Oral cavity	Salivary glands, saliva, tongue, uvula, oesophagus, tonsils
Renal system	Kidneys, urethra, urinary bladder
Other	Retina, adrenal glands, thyroid, adipose tissue

that the stimulation of the extracellular-signal-regulated kinase (ERK) cascade following binding of irisin to integrin receptors results in osteoblast proliferation and differentiation[12] Extensive immunohistochemical (IHC) analysis has revealed the presence of irisin in various tissues of the body (Table).[13]

Irisin in the periodontal regeneration

The PDL is a collagen containing soft connective tissue present between the inner wall of the socket and roots of the teeth.[14] Periodontitis is the destruction of the periodontium and is considered one of the most prevalent dental diseases worldwide.[15] Irisin has been found to be present in the periodontium and dental pulp regions in the rodent jaw, as well as in cultured human periodontal ligament cells (hPDLCs), human dental pulp cells (hDPCs) and primary human osteoblasts (hOBs). Expression of irisin is regulated in these tissues by mechanical stimulation, which shows that irisin may act in an autocrine, paracrine or endocrine manner in the oral cavity and alveolar bone tissue.[16] Treatment with recombinant irisin promotes the growth of hPDLCs along with an increase in migration and extracellular matrix formation. The hPDLCs treated with irisin showed increased deposition on type 1 collagen and enhanced secretion of proteins related to osteoblastogenesis, such as osteocalcin and leptin, along with an increase in the angiogenesis factors, such as vascular endothelial growth factor (VEGF). It also enhanced mineralisation of hPDLCs and secretion of osteocalcin, which is a marker of osteoblast differentiation.[7] A systematic review on the use of mesenchymal stem cells (MSC) for periodontal regeneration from preclinical animal models and humans found that MSC grafting enhances periodontal regeneration; hence periodontal cell therapy is beneficial for periodontal regeneration.[17]

Irisin in the alveolar bone regeneration and augmentation

Alveolar bone is an important component of the periodontium. Irisin has various effects on bone and bone cells, such as regulation of bone metabolism, increase in the production of bone marker genes, and increase in osteoblast differentiation.[18] It is detected in the alveolar bone and primary hOBs where treatment with recombinant irisin shows an increase in growth, migration and osteogenic behaviour of hOBs.[16] Irisin has an inductive effect on bone formation as it affects the bone matrix mineral secretion process of osteoblasts and induces osteoblast and osteocalcin production.[19] Experiments using dental bud stem cells (DBSC) cultured in osteogenic conditions with continuous irisin treatment showed several effects including an increase in the osteocalcin expression of DBSCs and an increase in the mineral matrix deposition (19). A recent study conducted on titanium implants in calvarial bone of mice found that treatment with irisin helps combat particle-induced inflammatory osteolysis of bone and restrains oxidative stress (OS) and receptor activator of nuclear factor kappa-B ligand (RANKL) production caused by titanium particles. Treatment with irisin can provide a potential strategy for the prevention of osteolysis and prosthetic loosening.[20] A recent systematic review with meta-analysis aimed at evaluating the effect of exercise and irisin injections on bone quality of osteoporotic mice, and found that exercise and injections of irisin showed improved bone quality in osteoporotic rats compared to the healthy ones; hence, irisin can mitigate bone loss as a result of osteoporosis.[21]

Irisin in cementum repair and regeneration

Cementum is a mineralised, avascular tissue that is an essential part of the dental attachment apparatus.[22] Ectomesenchymal cells called cementoblasts present during tooth development are responsible for the production of cementum and its regeneration.[23] Irisin has been shown to promote the differentiation of cementoblasts. Mineral induction of an immortalised mouse cementoblast (OCCM-30) cell line shows an elevated expression of PGC-1α, which is a precursor of irisin, as well, an increase in the cementoblast differentiation markers, such as Runx2, osterix and alkaline phosphatase (ALP). Cementoblast cell proliferation was also shown to be enhanced when treated with high-dose irisin for 72 hours.[24] The formation of mineralised nodules also increases under the influence of irisin, suggesting its important role in the mineralisation process of cementum as well as in the differentiation of cementoblasts. The p38 mitogen-activated protein kinase (MAPK) signalling pathway functions in the release of cytokines by macrophages and neutrophils and regulates functions, including cell proliferation, differentiation and apoptosis. It has been found that irisin exerts its promoting effects on cementoblast differentiation through the activity of p38 MAPK pathway.[24]

Irisin in vital pulp therapy

The dental pulp is a vascular integral component of the tooth responsible for defensive mechanisms and pulp vitality. Odontogenic differentiation of undifferentiated mesenchymal cells in pulp is a vital component of pulp therapy as it results in the formation of reparative dentin and repair of the pulp-dentin complex.[25] Irisin has recently been found to promote odontogenic differentiation in hDPCs and in the upregulation of important markers, such as dentin sialophosphoprotein (DSPP) and dentin matrix acidic phosphoprotein 1 (DMP-1). Treatment of hDPCs with irisin resulted in an increased ALP activity and mineral nodule formation, which shows that it can promote mineralisation and odontogenic differentiation. Angiogenesis is an essential component of healing and regeneration. Treatment with irisin increases the angiogenic potential in hDPCs and promotes important markers, such as fibroblast growth factor-1 (FGF-1) and VEGF, which are potent stimulators of angiogenesis and dental pulp repair.[6]

Irisin as a salivary biomarker in oral diseases

A study conducted by Aydin et al. suggested that saliva irisin concentrations were greatly increased compared to serum irisin levels after 45 minutes of showering in a Turkish bath. The high level of irisin in saliva compared to serum suggests a source of irisin in the salivary glands. Irisin was localised in all three major salivary glands, especially the striated ducts in the submandibular glands. It was found to be produced by acinar and ductal cells.[26] Salivary biomarkers are useful for the diagnosis of important cardiovascular diseases and infections, and also have diagnostic value in chronic diseases, such as diabetes, cancer and Alzheimer's.[27] A recent study investigated salivary irisin levels in RAS patients and found elevated levels of irisin in RAS patients compared to the healthy controls.[28] Another study conducted on patients with chronic periodontitis found that salivary irisin levels increased in chronic periodontitis, suggesting that irisin can act as a potential biomarker for chronic periodontitis.[8] Hence, irisin may act as an important biomarker for diseases, such as RAS, chronic periodontitis, diabetes, gestational diabetes, cardiovascular diseases and cancer, which could help in the early detection of such conditions, making it easier to diagnose and treat the patients in due time.

Irisin in facial muscle repair and healing

Irisin has many beneficial effects in the skeletal muscle growth and maintenance. It regulates genes related to muscle growth, such as insulin-like growth factor-1 (IGF-1).[29] It is involved in increased synthesis of proteins and production of satellite muscle cells. It was found that the treatment with recombinant irisin injection not only improves regeneration of skeletal muscle by increase in production of satellite cells, but also causes a decrease in protein degradation. This proves that irisin can act as a pro-myogenic factor.[30] Irisin can act as an important therapeutic agent in repair and healing of craniofacial muscles. In a recent study, it was reported that irisin may also be useful in preventing muscle atrophy. Treatment with irisin exerted an anti-atrophic effect on cultured immortalized mouse myoblasts (C2C12) cell line which were treated with dexamethasone, an inducer of muscular atrophy.[31]

Discussion

Irisin has extensive regulatory effects on the hard and soft tissues of the oral cavity on a molecular level. Various integral mechanisms, such as odontogenesis, angiogenesis, bone matrix formation, muscle cell regeneration, periodontal regeneration, and protective immune effects are regulated by irisin.

The current narrative review has its limitations as it covered research material published only in the English language.

Despite the limitations, however, the review is likely to add to the larger understanding about how irisin functions in different oral tissues, which may be the key to comprehending its role in formulating new therapeutic

clinical strategies in the future.

Irisin may prove to be an important molecule for regeneration of hard tissue defects in periodontal therapy as it can enhance the potential of periodontal cells in remodelling of the PDL and alveolar bone along with promotion of angiogenesis and neovascularization.

Irisin is an important potential therapeutic agent for future treatments of bony defects, such as bone loss in chronic periodontitis, bone loss in edentulous patients that requires bone augmentation before prosthetic placement and osseointegration in dental implants.

Therapeutic uses of irisin in regeneration of lost and damaged cementum from trauma or chronic periodontitis maybe a useful strategy in the future.

Irisin may also act as a new agent for use in vital pulp therapy due to its angiogenic and odontogenic effects.

Finally, genetic diseases, certain medical conditions or denervation-induced injuries can all contribute to craniofacial muscle atrophy. Irisin may act as an important therapeutic agent in the attenuation of such atrophic conditions.

Conclusion

Irisin is a promising candidate for therapeutic and diagnostic use in dentistry. Irisin exerts many beneficial effects on various oral tissues.

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