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The Role of Interleukin-8 in Thyroid Eye Disease and Potential Therapy: A Comprehensive Review

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ABSTRACT

Background: Thyroid Eye Disease [TED], also known as Graves' orbitopathy, is an autoimmune disorder marked by orbital inflammation and tissue remodeling. Interleukin-8 [IL-8], a pro-inflammatory cytokine, is increasingly recognized as crucial in TED's pathogenesis and progression. This review explores IL-8's role in TED, focusing on its contributions to inflammation, tissue remodeling, and fibrosis, and examines emerging therapies targeting IL-8 signaling.

Summary and Conclusion: A detailed analysis was conducted on IL-8's role in TED pathophysiology, emphasizing its impact on orbital inflammation, adipogenesis, angiogenesis, fibrosis, and hyaluronan production. Recent therapeutic advances targeting IL-8 were reviewed for their potential benefits in TED management. Results: IL-8 significantly contributes to TED by amplifying inflammation through immune cell recruitment and activation in orbital tissues. It promotes adipogenesis by facilitating pre-adipocyte differentiation, leading to orbital adipose tissue expansion. IL-8 drives angiogenesis, enhances vascularization, and exacerbates tissue damage. It also stimulates fibroblast activation and extracellular matrix deposition, contributing to fibrosis and tissue remodeling. Additionally, IL-8 increases hyaluronan production, causing tissue swelling and worsening TED symptoms. Therapeutic approaches inhibiting IL-8 signaling show promise in reducing inflammation and pathological tissue changes in TED. IL-8 is a key mediator of inflammation and tissue remodeling in TED, making it a promising therapeutic target. Targeting IL-8 signaling pathways offers a novel approach for TED management, though further research is needed to optimize treatments and understand the broader implications of IL-8 modulation in this disease.

Keywords: Thyroid Eye Disease, Interleukin-8; Graves' Orbitopathy

INTRODUCTION

A hydrocele is an unusual accumulation of fluid along the pathway of Thyroid eye disease [TED] is a debilitating condition associated with Graves' disease and is characterized by ocular manifestations, as eyelid retraction, proptosis, and diplopia. Although the exact etiology of TED remains elusive, growing evidence suggests that inflammatory mediators, including Interleukin-8 [IL-8], play a crucial role in the pathogenesis of the disease [1,2]. This comprehensive review explores the intricate relationship between IL-8 and TED, delving into the molecular mechanisms by which IL-8 contributes to orbital inflammation and tissue remodeling [3]. In addition, it examines the potential of IL-8 as a biomarker for disease activity and severity as well as its prognostic value in predicting treatment outcomes [4]. Furthermore, it discusses emerging therapeutic strategies targeting IL-8 and it's signaling pathways, offering promising avenues for future TED management and treatment [5].

This review sheds light on the critical role of interleukin-8 in thyroid eye disease pathogenesis and offers insights into its potential as a biomarker and therapeutic target. By elucidating the molecular mechanisms underlying IL-8 involvement in orbital inflammation and tissue remodeling, this comprehensive analysis paves the way for improved disease monitoring and novel treatment strategies in TED management.

Interleukin-8: The Architect of Inflammation:

IL-8 is a prototypical member of the CXC chemokine family, is a central orchestrator of inflammation and immune cell recruitment. Produced by myriad cell types, including leukocytes, muscles, adipose tissue, fibroblasts, and endothelial cells, IL-8 produces its biological effects by binding to its receptors CXCR1 and CXCR2, leading to the activation and migration of neutrophils, monocytes, and other immune effectors [4,6]. Beyond its essential role in acute inflammation, interleukin-8 has been involved in chronic inflammatory conditions, autoimmune diseases, and cancer, highlighting its multilateral functions in health and disease [7,8].

IL-8 signaling pathway is an essential component of the innate immune response, regulating the recruitment and activation of various immune cells at sites of inflammation. IL-8 is produced in response to inflammatory stimuli such as cytokines [e.g., TNF-α and IL-1β], bacterial products, and tissue injury [19, 0]. Upon secretion, IL-8 binds to two high-affinity G protein-coupled receptors, CXCR1 [IL-8RA] and CXCR2 [IL-8RB], which are expressed on the surface of various immune cells, including monocytes, neutrophils, and T lymphocytes [11].

Binding of IL-8 to CXCR1 and CXCR2 induces conformational changes in these receptors, leading to activation of downstream signaling pathways [12]. Once activated, CXCR1 and CXCR2 engage heterotrimeric G proteins, specifically Gαi, which results in dissociation of the Gα subunit from the Gβγ dimer. The released Gαi subunit inhibits adenylate cyclase, reducing cyclic AMP [cAMP] levels, while the Gβγ dimer activates phospholipase C [PLC]. This activation causes the hydrolysis of phosphatidylinositol 4,5-bisphosphate [PIP2] into inositol trisphosphate [IP3] and diacylglycerol [DAG] [13,14].

IP3 triggers the release of calcium ions [Ca^{2+}] from intracellular stores, particularly the endoplasmic reticulum, resulting in increased cytoplasmic Ca^{2+} levels. This elevated calcium concentration activates downstream signaling molecules, including protein kinase C [PKC][15]. Concurrently, DAG and PKC activation stimulates mitogen-activated protein kinase [MAPK] signaling pathways, including the extracellular signal-regulated kinase [ERK], c-Jun N-terminal kinase [JNK], and p38 MAPK pathways. These pathways regulate gene expression, cell proliferation, differentiation, and survival, highlighting the multifaceted roles of IL-8 in orchestrating immune responses and maintaining cellular homeostasis [14,15].

Similarities between interleukin-8 and insulin growth factor signaling pathways

Although IL-8 and insulin-like growth factor [IGF] signaling pathways serve distinct physiological functions, there are some notable similarities in their signaling cascades. Both pathways depend on certain cell surface receptors for receptor-mediated activation. IL-8 binds to its receptors CXCR1 and CXCR2, while IGF binds to insulin-like growth factor 1 receptor [IGF-1R] and insulin receptor [IR] [14]. Upon ligand binding, IL-8 and IGF receptors activate intracellular signaling cascades, such as the MAPK and phosphoinositide 3-kinase [PI3K]/Akt pathways, which regulate cellular processes such as proliferation, survival, and differentiation [15]. IL-8 and IGF are similar in the involvement of the G proteins. IL-8 receptors, particularly CXCR1 and CXCR2, activate heterotrimeric G proteins upon ligand binding, initiating downstream signaling events. Similarly, IGF-1R and IR can utilize G protein-coupled pathways under certain conditions, although their primary signaling mechanism involves receptor tyrosine kinase [RTK] activity [16]. Both pathways also modulate gene expression by activating transcription factors such as nuclear factor-kappa B [NF-κB] and activator protein 1 [AP-1], which regulate the expression of genes associated with inflammation, cell proliferation, and survival [10].

The activation of the IL-8 and IGF signaling pathways elicits diverse cellular responses, including cell migration, proliferation, differentiation, and survival. While IL-8 primarily regulates immune responses and inflammation, IGF signaling plays a crucial role in growth, development, and metabolism [11]. Additionally, both pathways exhibit crosstalk with other signaling pathways, amplifying or modulating cellular responses. For instance, IL-8 signaling can synergize with other cytokine pathways to enhance inflammation, whereas IGF signaling interacts with the mammalian target of rapamycin [mTOR] pathway to regulate cell growth and metabolism [5].

Similarities between interleukin-8 and TSH signaling pathways

While IL-8 and thyroid-stimulating hormone [TSH] signaling pathways serve distinct physiological functions, there are notable similarities in their signaling cascades. IL-8 produces its effects by binding to specific cell-surface receptors, primarily CXCR1 and CXCR2. Similarly, TSH binds to its cognate receptor, TSH receptor [TSHR], located on the surface of thyroid follicular cells [16]. Both IL-8 receptors [CXCR1 and CXCR2] and TSH receptors are G protein-coupled receptors [GPCRs]. Upon ligand binding, these receptors activate heterotrimeric G proteins, leading to downstream signaling events [10].

Activation of IL-8 receptors stimulates intracellular signaling cascades, including the mitogen-activated protein kinase MAPK and PI3K/Akt pathways. Similarly, activation of the TSH receptor triggers the activation of cAMP and PKA pathways, leading to gene transcription and thyroid hormone synthesis [14]. Additionally, both IL-8 and TSH signaling pathways modulate gene expression through the activation of transcription factors. IL-8 signaling can activate transcription factors, such as NF-κB and AP-1, leading to the expression of genes involved in inflammation and immune responses. In contrast, TSH signaling stimulates the expression of thyroid-specific genes such as thyroglobulin, thyroid peroxidase, and sodium-iodide symporter [NIS], which are crucial for thyroid hormone synthesis and secretion [15].

Cellular responses to these signaling pathways are also distinct and comparable. IL-8 signaling leads to chemotaxis, leukocyte activation, and inflammation, whereas TSH signaling regulates thyroid cell growth, differentiation, and hormone production, ultimately maintaining thyroid homeostasis and metabolic regulation [5]. Furthermore, both pathways exhibit crosstalk with other signaling pathways, amplifying or modulating cellular responses. For example, IL-8 signaling can interact with pathways such as NF-κB and Janus kinase/signal transducer and activator of transcription [JAK/STAT] to regulate inflammatory responses. TSH signaling can cross-talk with pathways involved in thyroid hormone synthesis, including IGF-1 pathway and the mammalian target of rapamycin [mTOR] pathway [11].

Interleukin-8 role in insulin resistance

IL-8 has been associated with the development and progression of insulin resistance, which is an essential feature of type 2 diabetes mellitus and metabolic syndrome. IL-8 plays, as a proinflammatory cytokine, has a central role in orchestrating the immune response to infection and tissue injury. Chronic low-grade inflammation, a hallmark of obesity and insulin resistance, cause the secretion of IL-8 and other inflammatory cytokines by adipose tissue, particularly visceral adipose tissue, in response to adipocyte hypertrophy and dysfunction [17]. In obese individuals, dynamic changes in adipose tissue, including increased production of inflammatory cytokines, such as IL-8, contribute to adipocyte dysfunction, impaired adipogenesis, and altered adipokine secretion patterns, leading to systemic insulin resistance [18].

IL-8 also interacts with adipokines, such as adiponectin and leptin, which regulate insulin sensitivity and energy homeostasis. Dysregulation of these signaling pathways, coupled with increased IL-8 production, disrupts insulin signaling in target tissues, further exacerbating insulin resistance [19]. IL-8 may also directly impair insulin signaling pathways in insulin-sensitive tissues such as skeletal muscle, liver, and adipose tissue. Studies have demonstrated that IL-8 inhibits insulin-stimulated glucose uptake in skeletal muscle cells and adipocytes by interfering with insulin signaling cascades, particularly PI3K/Akt pathway [20].

Akt activation plays a crucial role in glucose metabolism by promoting glucose uptake into cells through translocation of glucose transporter proteins, particularly GLUT4, to the cell membrane. IL-8-mediated inhibition of Akt signaling disrupts this process, impairing glucose uptake in insulin-sensitive tissues, and contributing to hyperglycemia and insulin resistance. Additionally, Akt phosphorylates and inhibits glycogen synthase kinase 3 [GSK-3], thereby promoting glycogen synthesis and inhibiting gluconeogenesis. IL-8-induced attenuation of Akt activity disrupts these processes, further exacerbating insulin resistance and glucose intolerance [21] and this process can be seen in Fig 1.

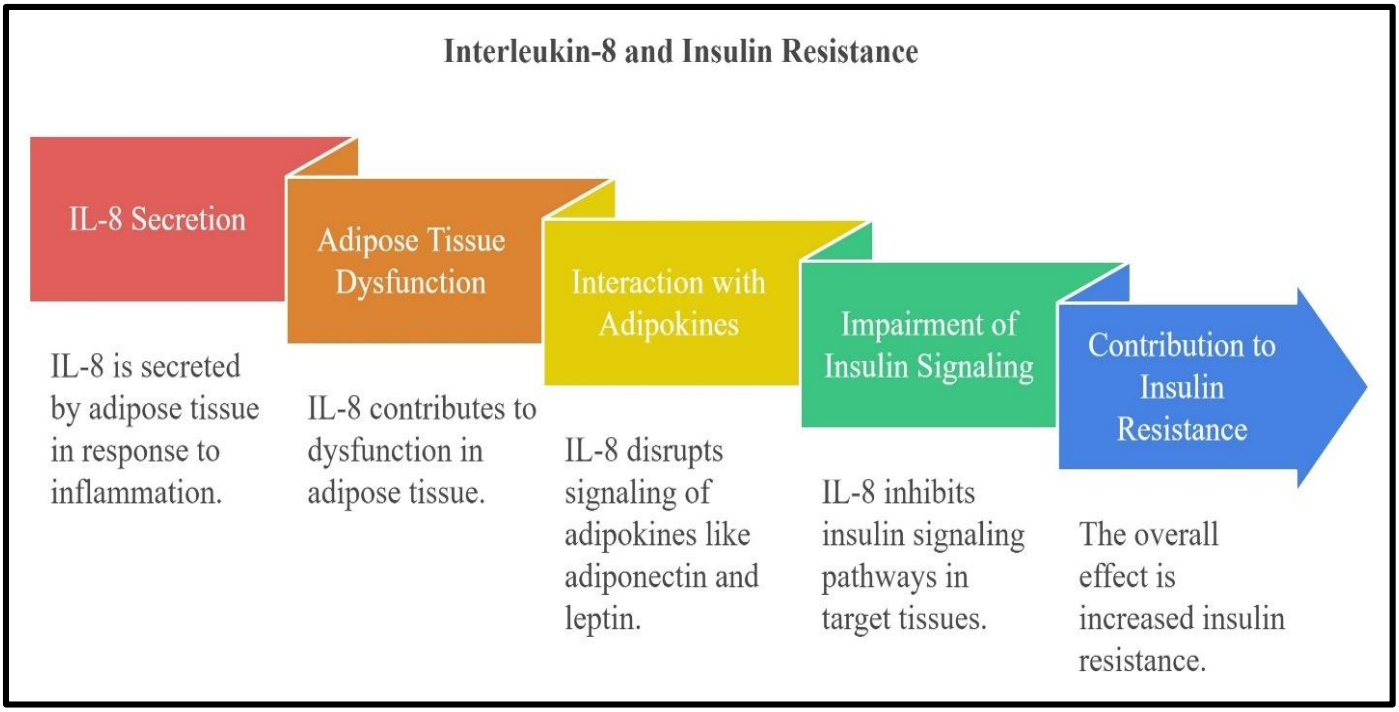

Figure [1]: Interleukin-8 and Insulin Resistance.

Interleukin-8 role in skeletal muscle hypertrophy

IL-8 may contribute to skeletal muscle hypertrophy through several mechanisms. The skeletal muscle, now recognized as an endocrine organ, secretes signaling molecules known as myokines. IL-8 is a myokine released by skeletal muscle fibers in response to exercise-induced stress or mechanical loading and plays a role in promoting muscle hypertrophy [22]. IL-8 may influence skeletal muscle growth by modulating satellite cells, which are muscle stem cells critical for repair and growth. Through IL-8 signaling, satellite cells may proliferate, differentiate, and fuse with existing muscle fibers, thereby enhancing muscle protein synthesis and hypertrophy [23].

IL-8 also exhibits angiogenic properties, stimulating the formation of new blood vessels. During skeletal muscle hypertrophy, increased vascularization is essential for delivering oxygen and nutrients to growing muscle fibers. IL-8-mediated angiogenesis supports muscle growth by improving blood flow and nutrient delivery [24]. While chronic inflammation is generally detrimental to muscle health, transient inflammation is necessary for muscle repair and growth. IL-8 contributes to the acute inflammatory response following exercise-induced muscle damage, recruiting immune cells and activating repair mechanisms that promote muscle hypertrophy [25].

Furthermore, IL-8 interacts with other growth factors and signaling pathways involved in muscle hypertrophy. For example, IL-8 can induce

the secretion of IGF-1, which is a potent stimulator of muscle protein synthesis. Additionally, IL-8 activates intracellular signaling cascades, such as MAPK pathway, which regulates gene expression and cell growth in skeletal muscles [14]. IL-8 may also directly influence muscle protein synthesis by activating pathways such as PI3K/Akt pathway, promoting the translation of messenger RNA [mRNA] into proteins, and contributing to muscle fiber growth and hypertrophy [20].

Interleukin-8 role in fibrosis

IL-8 plays an indirect but significant role in the fibrotic process through various mechanisms. As a potent chemoattractant, IL-8 promotes the recruitment of neutrophils and other immune cells to the sites of skeletal muscle injury or chronic inflammation. Upon recruitment, these neutrophils release pro-fibrotic cytokines and growth factors, such as transforming growth factor-beta [TGF-β], which stimulate fibroblast activation and collagen deposition, contributing to fibrosis [24]. Additionally, IL-8 plays a critical role in the activation of steroid receptor coactivators [SRCs], which are key regulators of gene transcription involved in fibrosis. By stimulating signaling pathways that upregulate and activate SRCs, IL-8 drives the transcription of fibrotic genes, promoting extracellular matrix production and tissue remodeling, which are hallmark features of the fibrotic process [26].

This mechanism aligns closely with the role of IGF-1, which also activates SRCs and enhances their co-activator functions. Both IL-8 and IGF-1 modulate SRC activity through their respective signaling pathways, leading to the increased expression of fibrotic genes and proliferation of myofibroblasts. This shared ability underscores the convergence of inflammatory and growth factor signaling in promoting fibrosis via SRC activation, highlighting a parallel relationship between IL-8 and IGF-1 in the context of skeletal muscle fibrosis [16].

Interleukin-8 role in adipogenesis

IL-8 significantly influences adipogenesis by interacting with key signaling molecules and pathways including Wnt5a, peroxisome proliferator-activated receptor gamma [PPARγ], and PI3K. IL-8 enhances the proliferation and differentiation of preadipocytes into mature adipocytes through modulating the activity of PPARγ which is a regulator of adipogenesis. IL-8 drives the transcription of adipogenic genes essential for adipose tissue development [20]. Moreover, IL-8 interacts with the PI3K pathway, an essential signaling cascade involved in cellular growth and differentiation, facilitating the adipogenic process. IL-8 balances adipocyte formation by modulating the Wnt5a pathway, which acts as an adipogenesis inhibitor and by countering Wnt5a's inhibitory effects [14].

IGF-1 also plays a pivotal role in adipogenesis, functioning similarly to IL-8, by enhancing PPARγ activity and activating the PI3K pathway. IGF-1 works synergistically with IL-8 to promote adipogenesis supports the proliferation and differentiation of preadipocytes [23]. These interactions mark the complex roles of IL-8 and IGF-1 in adipose tissue dynamics by integrating multiple signaling pathways to regulate adipose tissue expansion and function [21].

Interleukin-8 role in angiogenesis

IL-8 binds to its receptors CXCR1 and CXCR2 on endothelial cells, triggering activation of the PI3K/Akt pathway which promotes endothelial cell survival and proliferation, which are essential processes for the formation of new blood vessels [27]. In parallel, IL-8 activates PLC, leading to increased intracellular calcium levels and activation of protein kinase C [PKC], which enhances endothelial cell migration, a main step in the angiogenic process [28].

IL-8 stimulates FAK expression, a crucial step for the formation and turnover of focal adhesions which enhance cell motility and organization within the extracellular matrix, aiding endothelial cells to remodel their surroundings during blood vessel formation [26]. Through these interconnected pathways, IL-8 triggers a coordinated response that drives the complex angiogenesis process. This highlights its role in tumor vascularization and chronic inflammation [29].

Interleukin-8 role in hyaluronan production

IL-8 significantly influences hyaluronan production, a critical component of the extracellular matrix that plays a vital role in tissue hydration, elasticity, and repair. IL-8 activates fibroblasts and other cell types, enhancing HA synthesis by upregulating the expression of hyaluronan synthases, the enzymes responsible for its production. This process is mediated through signaling pathways, such as PI3K/Akt and MAPK, which are triggered upon IL-8 binding to its receptors, CXCR1 and CXCR2 [51]. The resulting elevated hyaluronan production increases water retention and tissue swelling, contributing to edema commonly observed in inflammatory conditions such as arthritis and TED [30].

In addition to its role in tissue swelling, hyaluronan serves as a scaffold for cellular migration and proliferation. This facilitates tissue remodeling and fibrosis in chronic inflammatory environments and exacerbates the pathological changes. IL-8's involvement in these processes underscores its dual role in promoting inflammation and driving disease progression under various conditions. The link between IL-8 and hyaluronan production highlights its importance in both physiological repair mechanisms and pathological tissue remodeling, making it a potential target for therapeutic intervention in diseases characterized by excessive inflammation and fibrosis [31].

Interleukin-8 role in hypoxia inducible factor

IL-8 exerts notable effects on hypoxia-inducible factor [HIF], a key transcription factor responsible for cellular adaptation to low oxygen levels. Under hypoxic conditions, HIF-1α, the active subunit of HIF, accumulates and translocates to the nucleus where it binds to hypoxia-response elements [HREs] in the promoters of genes involved in angiogenesis, glycolysis, and cell survival. IL-8 can directly induce the expression of HIF-1α, promoting its accumulation, and enhance its transcriptional activity. Moreover, IL-8 contributes to the stabilization of HIF-1α by inhibiting its degradation via the proteasome pathway [15].

In addition to its direct effects on HIF-1α, IL-8 plays a crucial role in stimulating angiogenesis, a process that is tightly regulated by HIF-1α. IL-8 upregulates the expression of vascular endothelial growth factor [VEGF], a key mediator of angiogenesis. This interaction underscores IL-8's role in facilitating cellular and tissue adaptations to hypoxic environments. By influencing HIF-1α activity and promoting VEGF expression [28,30].

Interleukin-8 role in Dry eye disease and Thyroid Eye Disease

IL-8, a proinflammatory cytokine, is upregulated in the tears and conjunctival epithelium of patients with Dry Eye Disease [DED], therefore it plays an important role in the pathogenesis of DED. IL-8 promotes the recruitment and activation of neutrophils and other immune cells to the ocular surface, sustain inflammation and exacerbating tissue damage. Moreover, IL-8 stimulates the production of matrix metalloproteinases [MMPs], which are enzymes that degrade the extracellular matrix and compromise the integrity of the ocular surface. This degradation contributes to tear film instability and worsens ocular discomfort [4,20].

Additionally, IL-8 may increase pain perception by sensitizing corneal nerves, further intensifying ocular discomfort. Elevated IL-8 levels in the tears and orbital tissues of patients with TED also indicate its involvement in exacerbating inflammation and tissue remodeling. In TED, IL-8 disrupts tear film stability, aggravates dry eye symptoms, and compromises the overall ocular surface health. Targeting the IL-8 signaling pathway presents a promising therapeutic approach for managing ocular surface inflammation and alleviating symptoms in patients with DED and TED. Understanding the role of IL-8 in these conditions provides valuable insights into their pathogenesis and guides the development of novel treatments aimed at restoring ocular surface homeostasis and improving the quality of life of affected individuals [3], as shown in Figure 2.

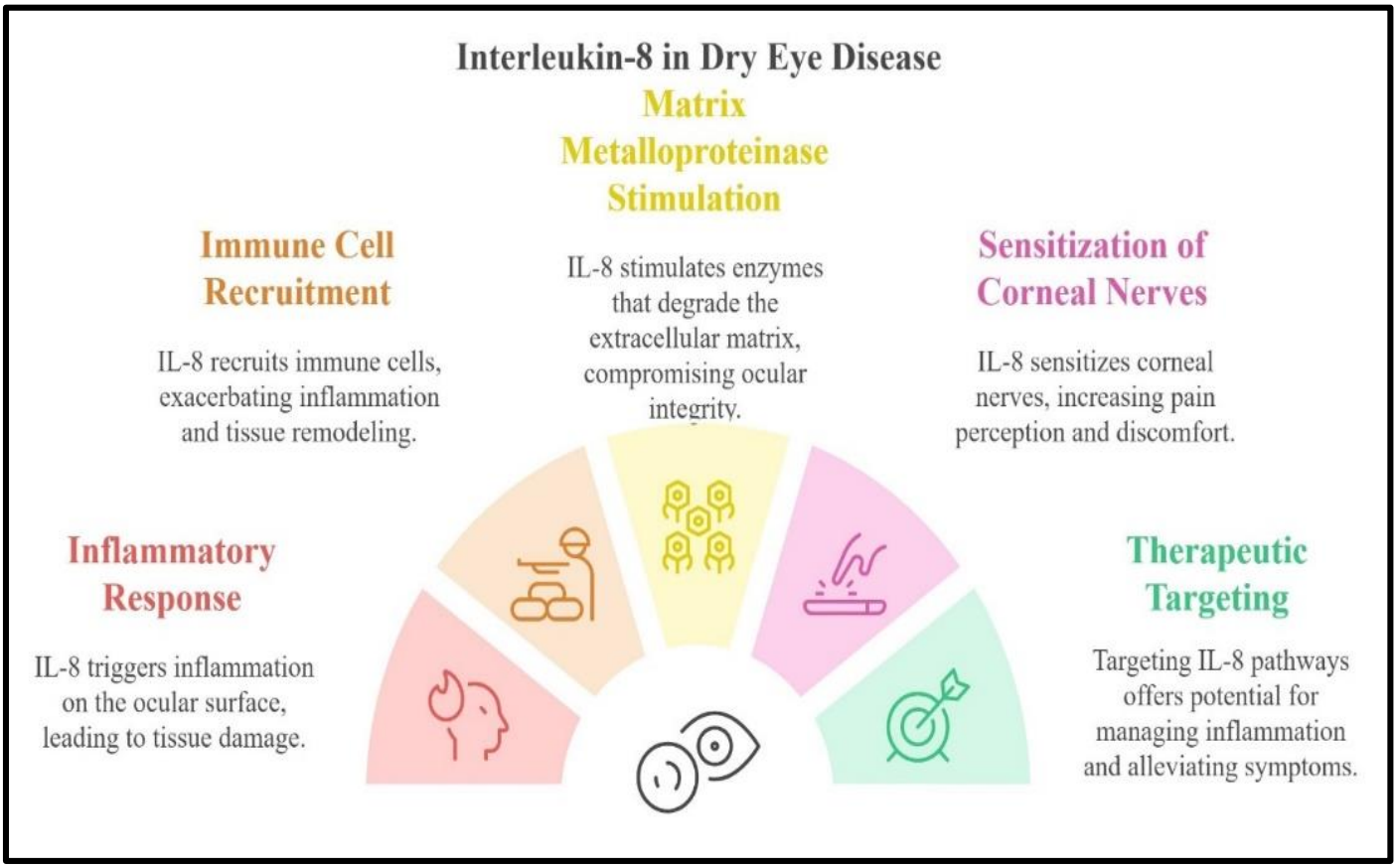

Figure [2]: Interleukin-8 role in Dry eye

Interleukin-8 orchestra of cross talks between muscle and adipose tissues

Skeletal muscle secretes IL-8 in response to various stimuli including exercise, inflammation, and oxidative stress. IL-8 production by both skeletal muscle and adipose tissue can exert autocrine and paracrine effects such as regulating metabolic homeostasis and modulating the immune response. Moreover, IL-8 can influence muscle metabolism and inflammation, while also acting on adipose tissue to affect adipocyte metabolism and inflammatory states [22].

Conversely, adipose tissue, particularly visceral adipose tissue, is a significant source of IL-8, especially in conditions such as obesity and metabolic syndrome. Adipose-derived IL-8 contributes to chronic low-grade inflammation, a hallmark of these conditions, and exacerbates insulin resistance and metabolic dysfunction, thereby impacting systemic health [61]. This bidirectional relationship highlights the crosstalk between skeletal muscle and adipose tissue mediated by IL-8 and its essential role in integrating metabolic and inflammatory signaling [25].

Interleukin-8 contribution for side effects of teprotumumab

IL-8 may indirectly contribute to some side effects associated with teprotumumab, a monoclonal antibody targeting IGF-1 Receptor. IL-8's pro-inflammatory actions, including the recruitment and activation of immune cells, could exacerbate systemic inflammation induced by teprotumumab, potentially contributing to side effects such as fever, fatigue, or flu-like symptoms. Additionally, IL-8 is a key mediator of skin inflammation and immune cell infiltration, which may worsen any dermatological reactions associated with teprotumumab, although these are not common side effects of the drug [28].

IL-8's role in the inflammatory response within the gastrointestinal tract may also intersect with gastrointestinal disturbances reported during teprotumumab treatment, such as nausea, diarrhea, or discomfort. IL-8 may exacerbate these symptoms by contributing to the mucosal inflammation. Similarly, IL-8's ability to stimulate immune cell infiltration into inflamed tissues could influence muscle inflammation and damage, potentially playing a role in the musculoskeletal symptoms experienced by some patients, although these are not commonly reported side effects of teprotumumab. IL-8 may contribute to inflammation and tissue damage within the auditory system, potentially affecting the delicate structures of the inner ear and leading to sensorineural hearing loss. Chronic inflammation mediated by IL-8 could theoretically compound the hearing-related side effects of teprotumumab, although the drug primarily affects pathways associated with IGF-1R signaling. IGF-1 plays a role in cellular processes related to auditory function, and disruption of IGF-1R signaling by teprotumumab could indirectly influence auditory health [20].

IL-8 has also been implicated in inflammatory processes underlying insulin resistance and is commonly associated with obesity and metabolic syndrome. Elevated IL-8 levels impair insulin signaling pathways and exacerbate the dysregulation of glucose metabolism. Targeting of IGF-1R by teprotumumab may indirectly influence insulin resistance, as IGF-1R signaling is linked to insulin sensitivity and glucose metabolism. Disruptions in this pathway could potentially worsen insulin resistance, further highlighting the complex interplay between IL-8, teprotumumab, and metabolic health [21]. Finally, IL-8's association with neuro-inflammation has been linked to poorer cognition in elderly individuals, affecting executive function, attention, visuospatial abilities, memory, cognitive speed, and motor function. Similarly, teprotumumab may influence cognitive decline by blocking IGF-1R, a pathway that is critical for neuronal survival and function. Understanding the interactions among IL-8, teprotumumab, inflammation, and immune modulation offers insights into their potential implications for cognitive health and overall patient outcomes [11,22], as shown in Fig 3.

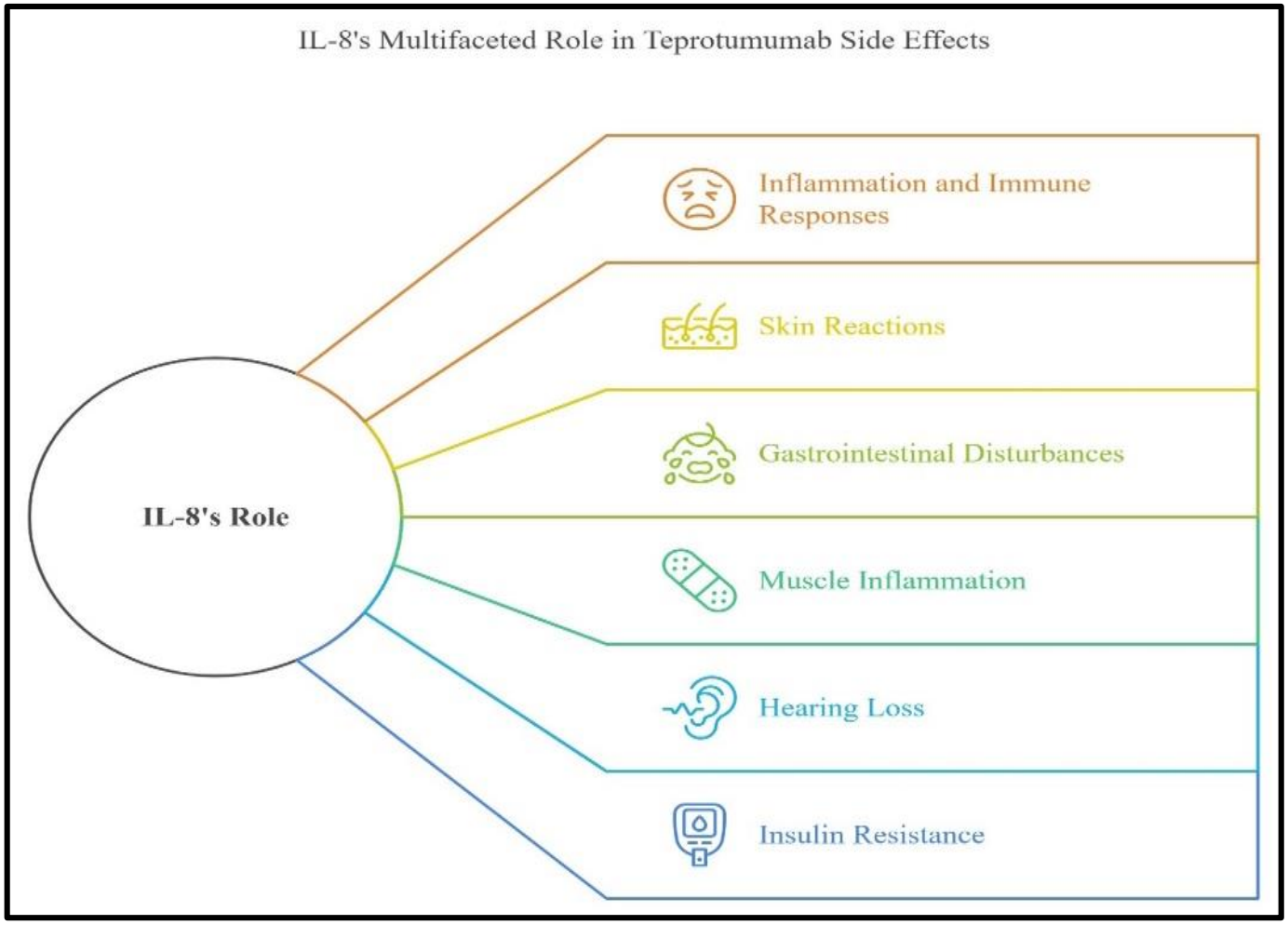

Figure [3]: Interleukin-8 side effects

Interleukin-8 inhibitors as a promising therapy for Thyroid eye disease

IL-8 inhibitors present a promising avenue in immunotherapy for conditions characterized by excessive inflammation. IL-8, also known as CXCL8, is a chemokine produced by various cell types in response to inflammatory stimuli and primarily functions to recruit neutrophils to sites of inflammation. However, dysregulated IL-8 production can result in chronic inflammation, contributing to the pathogenesis of diseases, such as rheumatoid arthritis, asthma, and certain cancers. By blocking the interaction between IL-8 and its receptors CXCR1 and CXCR2, IL-8 inhibitors impede neutrophil recruitment, thereby mitigating the inflammatory response [27]. These inhibitors can be administered through intravenous infusion, subcutaneous injection, or oral administration depending on the specific drug and formulation.

Despite their potential, IL-8 inhibitors may be associated with side effects including infusion reactions, injection site reactions, gastrointestinal disturbances, and an increased risk of infections due to impaired neutrophil function [17]. These risks underscore the importance of optimizing the efficacy and safety profile of IL-8 inhibitors. Continued research in this area aims to maximize therapeutic benefits while minimizing adverse effects, ensuring that IL-8 inhibitors can effectively manage inflammation-driven conditions without compromising patient safety [28] see Fig 4.

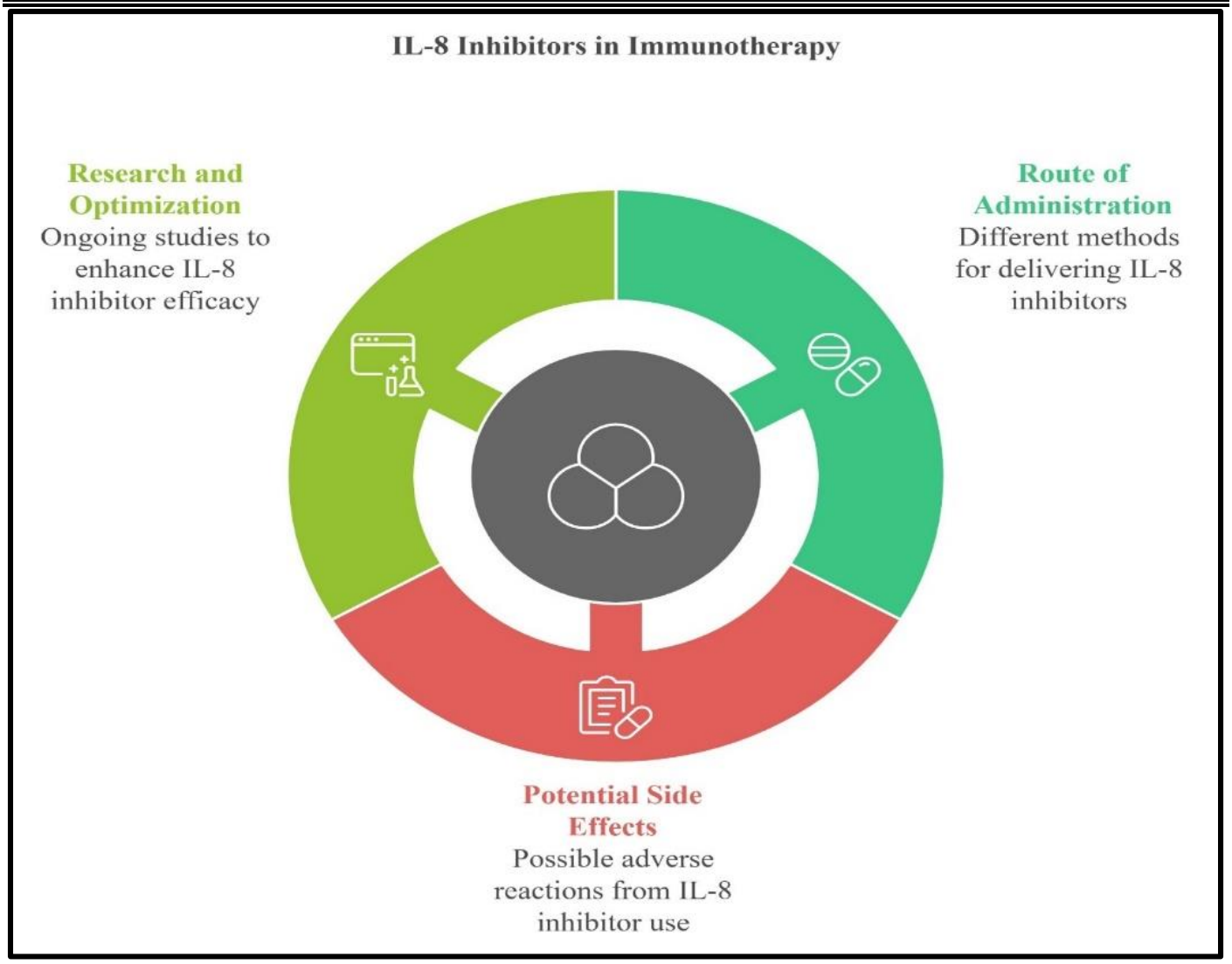

Figure [4]: IL-8 Inhibitors in Immunotherapy

DISCUSSION AND CONCLUSION

TED, also known as Graves' ophthalmopathy, is an autoimmune condition characterized by inflammation and swelling of eye tissues. IL-8 plays a critical role in multiple aspects of TED pathophysiology, including adipogenesis, angiogenesis, muscle hypertrophy, fibrosis, inflammation, insulin resistance, and hyaluronan production. IL-8 shares some similarities with TSH in its effects on thyroid function, as both can stimulate thyroid hormone production, potentially contributing to the hyperthyroidism observed in TED. Additionally, IL-8 interacts with IGF-1 signaling pathway, modulating cell proliferation, survival, and differentiation, which contribute to the tissue remodeling characteristics of TED [17,27]. In adipogenesis, IL-8 promotes the differentiation of orbital preadipocytes into mature adipocytes, leading to the expansion of adipose tissue commonly observed in TED. IL-8 also enhances angiogenesis by promoting the formation of new blood vessels in the orbit, which exacerbates inflammation and tissue damage. Muscle hypertrophy, a hallmark of TED, is driven in part by IL-8, contributing to the enlargement of extraocular muscles, causing proptosis and restricted eye movement. Fibrotic changes in TED, such as eyelid retraction and limited motility, are linked to IL-8-mediated fibroblast activation and collagen deposition [28].

As a potent pro-inflammatory cytokine, IL-8 recruits' immune cells to the orbit and amplifies the inflammatory response in TED. Its involvement in insulin resistance further compounds the metabolic abnormalities in patients with TED. IL-8 also stimulates hyaluronan synthesis by orbital fibroblasts, resulting in soft tissue swelling owing to hyaluronan accumulation. This cytokine plays a role in the interplay between muscle and adipose tissue, contributing to the inflammatory environment in the orbit. Furthermore, IL-8-mediated inflammation in the lacrimal gland and ocular surface contributes to tear film instability and ocular surface damage, exacerbating dry eye syndrome, a common complication of TED [3, 15].

Orbital fibroblasts are the primary source of IL-8 production in TED, but immune cells, such as T lymphocytes, along with muscle and adipose tissue, also contribute to its production. A vicious cycle of IL-8 production exists in TED, where IL-8 from one cell type stimulates its production in others, perpetuating inflammation and tissue damage. Teprotumumab, a monoclonal antibody targeting IGF-1R, has shown promise for the treatment of TED. However, side effects, such as muscle spasms, diarrhea, fatigue, and hyperglycemia, may involve IL-8-mediated pathways. These findings highlight IL-8's central role in TED, and its potential as a therapeutic target. Although IL-8 inhibition offers promise, further research is required to fully elucidate its complex roles and optimize treatment strategies for TED [4].

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