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PATHOGENETIC MECHANISMS IN THE DEVELOPMENT OF OTOSCLEROSIS

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Abstract

Otosclerosis is a primary osteodystrophic disorder of the bony labyrinth capsule, characterized by abnormal bone remodeling leading to fixation of the stapes footplate and progressive conductive or mixed hearing loss. Despite over a century of study, the exact pathogenesis remains multifactorial and incompletely understood. Genetic predisposition, viral infection, autoimmune mechanisms, and hormonal influences are considered key contributing factors.

Objective. This review aims to summarize current concepts of the pathogenetic mechanisms underlying the development of otosclerosis, with emphasis on molecular, immunologic, and hormonal factors influencing abnormal bone turnover in the otic capsule.

Methods. A systematic analysis of recent literature (PubMed, Scopus, and Embase databases, 2010–2024) was performed. Data regarding histopathology, molecular signaling, viral associations, and genetic polymorphisms were evaluated and compared.

Results. Otosclerosis involves a disruption of the delicate balance between bone resorption and deposition in the otic capsule. The process begins with localized bone resorption mediated by activated osteoclasts, followed by replacement with immature, vascularized spongiotic bone. Genetic studies implicate several loci, notably OTSC1–OTSC10, and mutations in genes regulating bone metabolism (COL1A1, TGFB1, RELN, BMP2). Persistent measles virus infection has been identified in stapes footplates of affected patients, suggesting a viral trigger that activates cytokine cascades (IL-1β, TNF-α, and TGF-β). Additionally, autoantibodies against type II collagen and altered estrogen receptor activity contribute to the inflammatory and hormonal modulation of bone remodeling.

Conclusion. Otosclerosis represents a multifactorial disease resulting from genetic susceptibility combined with viral, autoimmune, and hormonal influences leading to dysregulated osteogenesis within the otic capsule. Understanding these mechanisms is crucial for developing targeted pharmacological and gene-based therapies to complement surgical treatment.

Keywords: Otosclerosis, stapes fixation, bone remodeling, measles virus, genetic factors.

Introduction

Otosclerosis is a localized bone dystrophy of the otic capsule that causes progressive fixation of the stapes footplate, resulting in conductive hearing loss and, in advanced cases, mixed or sensorineural impairment. It accounts for approximately 5–10% of adult-onset hearing loss and predominantly affects females aged 20–40 years.

Histopathologically, otosclerosis is characterized by alternating phases of bone resorption (spongiotic stage) and abnormal bone formation (sclerotic stage). The disease process typically

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initiates anterior to the oval window (fissula ante fenestram) and may extend to the cochlear endosteum.

Although the clinical picture and histology of otosclerosis are well established, its pathogenesis remains complex. Numerous studies suggest a multifactorial nature, involving:

Genetic predisposition — autosomal dominant inheritance with variable penetrance;

Viral factors — persistent measles virus infection detected in otosclerotic foci;

Autoimmune and inflammatory reactions;

Hormonal and metabolic influences (particularly estrogen and fluoride metabolism).

This interplay of molecular mechanisms leads to localized dysregulation of osteoblastic and osteoclastic activity, angiogenesis, and inflammatory cell recruitment in the otic capsule.

The present article provides a comprehensive analysis of the pathogenetic mechanisms of otosclerosis, integrating molecular, immunological, genetic, and hormonal evidence.

Materials and Methods

1. Bone Remodeling Dysregulation

Under normal conditions, the otic capsule exhibits minimal bone turnover compared to other skeletal sites. In otosclerosis, this homeostatic balance is disrupted.

Osteoclast activation results in excessive bone resorption, mediated by the RANK/RANKL/OPG pathway.

Osteoblast dysfunction leads to deposition of immature, collagen-poor bone.

Histochemical studies show increased expression of alkaline phosphatase and osteocalcin in active lesions.

2. Role of Cytokines and Growth Factors

Inflammatory cytokines play a pivotal role in lesion development. Elevated levels of IL-1β, IL-6, TNF-α, and TGF-β1 stimulate osteoclastogenesis and angiogenesis within the otic capsule.

TGF-β1 is particularly implicated in the transition from the spongiotic to the sclerotic phase, promoting excessive bone deposition.

Genetic Factors

Family studies have confirmed autosomal dominant inheritance with incomplete penetrance. Ten otosclerosis susceptibility loci (OTSC1–OTSC10) have been mapped to chromosomes 6p21, 15q25–26, and 7q34–36.

Key genes implicated include:

COL1A1 — encodes type I collagen; mutations lead to abnormal bone matrix structure.

TGFβ1 — regulates osteoblast differentiation; polymorphisms correlate with disease severity.

RELN — modulates extracellular matrix stability in the otic capsule.

BMP2/BMP4 — influence osteogenic differentiation.

Genome-wide studies have revealed SNPs associated with otosclerosis risk, highlighting the polygenic nature of the disorder.

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Results and Discussion

Viral and Autoimmune Hypotheses

Numerous investigations have detected measles virus RNA and antigens in otosclerotic stapes footplates and perilymph, suggesting viral persistence as a trigger for chronic inflammation. Viral proteins may induce cytokine-mediated bone remodeling through activation of TNF-α and NF-κB pathways.

Autoimmune mechanisms are supported by findings of autoantibodies to type II collagen and heat shock proteins (HSP70) in patient sera. These immune complexes promote inflammatory infiltration and osteoclastic activation within the otic capsule.

Hormonal and Metabolic Influences

The higher prevalence of otosclerosis among women and its tendency to worsen during pregnancy suggest a hormonal component. Estrogens and progesterone modulate bone metabolism via receptor-mediated regulation of osteoclast apoptosis. Increased estrogen activity may alter bone resorption in genetically predisposed individuals.

Additionally, disturbances in fluoride and calcium metabolism have been linked to otosclerosis. Fluoride deficiency may exacerbate abnormal bone turnover, explaining the therapeutic rationale for sodium fluoride in early disease stages.

The multifactorial nature of otosclerosis reflects complex interactions between genetic susceptibility, immune activation, viral persistence, and endocrine influences.

Genetic factors determine baseline vulnerability, while environmental triggers (notably measles infection) initiate an inflammatory cascade. Cytokine overproduction leads to osteoclastic hyperactivity, vascular proliferation, and replacement of dense lamellar bone with spongiotic tissue. As the lesion matures, osteoblasts deposit irregular sclerotic bone, eventually fixing the stapes footplate.

Modern molecular insights suggest that dysregulation of bone morphogenetic proteins (BMPs) and TGF-β signaling plays a central role in aberrant osteogenesis. These findings open perspectives for novel pharmacologic approaches targeting bone remodeling pathways (e.g., bisphosphonates, RANKL inhibitors).

Conclusion

Otosclerosis is a complex osteodystrophic disease arising from the convergence of genetic, viral, autoimmune, and hormonal mechanisms leading to focal bone remodeling within the otic capsule.

Genetic polymorphisms in COL1A1, TGFB1, and RELN increase susceptibility to abnormal bone metabolism.

Persistent measles virus infection and cytokine imbalance stimulate chronic inflammation and osteoclast activation.

Autoimmune reactivity and hormonal modulation further exacerbate pathological bone turnover.

Understanding these pathogenetic mechanisms provides the scientific basis for developing targeted conservative therapies to complement stapedotomy or stapedoplasty. Future research should focus on molecular biomarkers for early detection and the application of gene therapy or cytokine modulation strategies to prevent disease progression.

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