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Exploring Fumarate Hydratase-Deficient Uterine Leiomyomas

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Abstract

Fumarate Hydratase-Deficient Uterine Leiomyomas (FH-deficient UL) represent a unique subset of uterine leiomyomas associated with hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome. This comprehensive review delves into the molecular mechanisms, clinical manifestations, diagnosis, management, and emerging therapeutic strategies for FH-deficient UL. Loss of function mutations in the FH gene lead to the accumulation of fumarate, triggering dysregulation of hypoxia-inducible factor (HIF) pathways and promoting tumorigenesis. Clinically, FH-deficient UL often present with multiple, large leiomyomas at a young age, accompanied by symptoms such as menorrhagia and pelvic pain. Diagnosis relies on a combination of clinical, radiological, and histopathological findings, with genetic testing confirming HLRCC syndrome. Management necessitates a multidisciplinary approach, incorporating surgical intervention and close surveillance. Emerging targeted therapies offer promise but require further investigation. This review underscores the importance of continued research and collaboration to enhance our understanding and management of FH-deficient UL.

Keywords: fumarate hydratase; uterine leiomyomas; hereditary leiomyomatosis; renal cell carcinoma syndrome; hypoxia-inducible factor; molecular mechanisms; diagnosis; management; targeted therapy

Introduction

Uterine leiomyomas, commonly known as fibroids, are benign smooth muscle tumors of the uterus. While often asymptomatic, they can lead to significant morbidity, including heavy menstrual bleeding, pelvic pain, and reproductive dysfunction [7]. Fumarate hydratase (FH) deficiency is a rare genetic condition associated with the development of uterine leiomyomas [8]. This review aims to explore the molecular mechanisms, clinical manifestations, diagnosis, management, and emerging therapeutic strategies for FH-deficient uterine leiomyomas.

Molecular Mechanisms

FH is a key enzyme in the tricarboxylic acid (TCA) cycle, which plays a central role in cellular metabolism [9]. Its primary function is to catalyze the conversion of fumarate to malate. Loss of FH function due to genetic mutations results in the accumulation of fumarate within cells [10]. Elevated fumarate levels inhibit prolyl hydroxylases (PHDs), leading to the stabilization of hypoxia-inducible factors (HIFs) [11]. Dysregulation of HIF signaling pathways promotes tumorigenesis by enhancing cell proliferation, angiogenesis, and metabolic reprogramming. Additionally, fumarate accumulation can induce oxidative stress and DNA damage, further contributing to tumorigenesis [12].

Clinical Manifestations

FH-deficient uterine leiomyomas typically occur in the context of hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome, an autosomal dominant disorder caused by germline mutations in the FH gene [1]. HLRCC is characterized by the development of multiple cutaneous leiomyomas, renal tumours, and uterine leiomyomas at a young age [2]. Uterine leiomyomas in HLRCC tend to be numerous, large, and associated with early-onset symptoms such as menorrhagia, pelvic pain, and pressure symptoms due to their size and location [3]. The aggressive nature of FH-deficient tumours necessitates careful monitoring and management to prevent complications such as rapid tumour growth and malignant transformation.

Diagnosis

The diagnosis of FH-deficient uterine leiomyomas relies on a combination of clinical, radiological, and histopathological findings [4]. Patients with a suggestive clinical history of HLRCC, including a family history of early-onset uterine leiomyomas or renal tumours, should undergo genetic testing for FH mutations [5]. Imaging studies, such as pelvic ultrasound and magnetic resonance imaging (MRI), are useful for assessing the size, number, and location of uterine leiomyomas [6]. Histological examination of leiomyoma tissue typically reveals characteristic features, including the presence of prominent nucleoli, peri nucleolar halos, and eosinophilic cytoplasmic inclusions, which can aid in distinguishing FH-deficient leiomyomas from sporadic fibroids [7].

Management

Management of FH-deficient uterine leiomyomas requires a multidisciplinary approach involving gynecologists, medical geneticists, and oncologists [8]. Symptomatic patients may benefit from surgical intervention, including hysterectomy or myomectomy, to alleviate symptoms and reduce the risk of complications [9]. Close surveillance with regular imaging and renal function tests is essential for early detection of tumour recurrence or metastasis, particularly in patients with HLRCC-associated renal cell carcinoma [10]. Emerging targeted therapies aimed at restoring metabolic dysregulation and inhibiting HIF signaling pathways, such as HIF inhibitors and metabolic modulators, hold promise as potential therapeutic options for FH-deficient tumours but require further evaluation in clinical trials to assess their efficacy and safety profiles [11].

Conclusion

FH-deficient uterine leiomyomas represent a distinct subset of fibroids associated with HLRCC syndrome; a rare genetic disorder characterized by germline mutations in the FH gene [12]. Understanding the molecular mechanisms underlying FH deficiency provides valuable insights into the pathogenesis of these tumours and offers potential targets for therapeutic intervention. Further research is needed to elucidate the natural history of FH-deficient uterine leiomyomas and to develop personalized treatment strategies aimed at improving outcomes for affected individuals. Close collaboration between clinicians, researchers, and patients is essential for advancing our understanding and management of this rare but clinically significant condition.

Conflict of Interest

The authors declare no conflicts of interest.

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