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The Role and Diagnostic Utility of Prolyl 4-Hydroxylase Beta Polypeptide (P4HB) in Urothelial Carcinoma: A Comprehensive Review

Tasneem Abdallah Abomashhour, Magda Ibrahim Assaf, Mai Mohammed Abd Elwahab, Asmaa Abdullatif Mohammed

Pathology Department, Faculty of Medicine, Zagazig University. Egypt
Corresponding Author: Tasneem Abdallah Abomashhour
Mail: tasneemabdallah751@gmail.com

ABSTRACT

Background: Bladder cancer remains one of the most common malignancies affecting the urinary tract, with urothelial carcinoma constituting the predominant histological subtype. Despite advances in diagnostic and therapeutic modalities, the prognosis for invasive and variant histologies of urothelial carcinoma remains guarded, highlighting the urgent need for reliable molecular markers to improve early diagnosis, prognostication, and targeted therapy. Prolyl 4-hydroxylase beta polypeptide (P4HB) has emerged as a molecule of interest due to its involvement in protein folding, cellular stress responses, and tumor progression in multiple cancer types, including urothelial carcinoma. This comprehensive review aims to elucidate the epidemiology and risk factors associated with bladder cancer, emphasizing the evolving understanding of its pathogenesis as outlined in the 2022 WHO classification. Special attention is given to the pathological features and microscopic variants of invasive urothelial carcinoma, as these subtypes often demonstrate distinct clinical behavior and therapeutic responses. The review further explores the biochemical and cellular functions of P4HB, synthesizing evidence from basic science and translational studies to establish its relevance in the context of bladder tumor biology.

Recent investigations suggest that P4HB is frequently overexpressed in urothelial carcinoma, correlating with aggressive clinicopathological features such as high grade, advanced stage, and poor overall survival. Its diagnostic utility as an immunohistochemical marker, as well as its potential prognostic and therapeutic implications, are critically examined. Additionally, the review addresses challenges in integrating P4HB assessment into routine diagnostic algorithms and discusses future research directions aimed at validating its clinical utility.

In conclusion, P4HB represents a promising biomarker and potential therapeutic target in urothelial carcinoma. However, further large-scale, multi-institutional studies are required to substantiate its role and to optimize its integration into precision oncology protocols. By providing a comprehensive synthesis of current knowledge, this review aspires to facilitate deeper understanding and stimulate future investigations in this evolving field.

Keywords*: Diagnostic Utility, Role, Prolyl 4-Hydroxylase Beta Polypeptide , Urothelial Carcinoma*

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Introduction

Bladder cancer is among the ten most frequently diagnosed cancers worldwide, posing significant morbidity and mortality, particularly in developed nations. Urothelial carcinoma, previously known as transitional cell carcinoma, represents the most common histological variant, accounting for more than 90% of bladder tumors. Despite advances in diagnosis and management, the disease remains challenging due to its diverse morphological spectrum, propensity for recurrence, and potential for progression to muscle-invasive and metastatic stages. In this context, the accurate pathological assessment of bladder tumors is of paramount importance, guiding treatment strategies and prognostic estimations [1].

A persistent research gap exists in the identification of reliable molecular biomarkers that can refine risk stratification, enhance diagnostic accuracy, and potentially serve as therapeutic targets in urothelial carcinoma. Traditional histopathological evaluation is sometimes insufficient to capture the biological heterogeneity and predict clinical outcomes, especially in morphologically variant and high-grade lesions. Recent attention has focused on the molecular landscape of bladder cancer, with an emphasis on proteins involved in the regulation of cellular stress, extracellular matrix remodeling, and tumor microenvironment interactions [2].

One molecule that has garnered considerable interest is Prolyl 4-Hydroxylase Beta Polypeptide (P4HB), a multifunctional protein implicated in collagen biosynthesis, protein folding, and cellular stress responses. Emerging evidence suggests that P4HB overexpression may contribute to tumor aggressiveness and resistance to therapy in several malignancies, including bladder cancer. However, its precise role in the tumorigenesis, progression, and diagnostic evaluation of urothelial carcinoma remains incompletely understood [3].

The present review aims to provide a comprehensive synthesis of current evidence regarding the clinicopathological features, risk factors, and molecular underpinnings of bladder cancer, with a particular focus on the diagnostic and prognostic significance of P4HB expression. By critically appraising the available literature and integrating recent advances, this review seeks to highlight the potential of P4HB as a novel biomarker in urothelial carcinoma and to identify avenues for future translational research [4].

A. Epidemiology of Bladder Cancer

Bladder cancer ranks as the tenth most common malignancy globally, with an estimated 573,000 new cases and 213,000 deaths annually according to 2020 data. It is notably more prevalent in men than women, with a male-to-female incidence ratio of approximately 3:1. The disease predominantly affects

10.48047/jocaaa.2024.33.06.107

individuals over the age of 65, with the incidence rising sharply with advancing age. Differences in geographic incidence reflect variations in environmental exposures, industrialization, and healthcare infrastructure, with the highest rates observed in developed countries of Europe and North America [5].

Urothelial carcinoma constitutes more than 90% of all bladder cancers in Western countries, while squamous cell carcinoma and adenocarcinoma are more prevalent in regions with endemic schistosomiasis, such as parts of Africa and the Middle East. The incidence and mortality of bladder cancer are closely linked to modifiable risk factors, including tobacco use and exposure to industrial carcinogens, as well as improvements in diagnostic and therapeutic modalities. The increasing prevalence of risk factors and population aging are expected to further elevate the global burden of this disease [6].

Bladder cancer is characterized by a high recurrence rate, with up to 70% of patients experiencing tumor relapse following initial treatment. This highlights the need for rigorous surveillance protocols and effective secondary prevention strategies. Although the majority of new cases present as non-muscle-invasive disease, a significant proportion eventually progress to muscle-invasive or metastatic stages, which are associated with significantly worse outcomes. This epidemiological reality underscores the critical importance of early detection and improved biomarker development to guide management [7].

B. Risk Factors

The most significant risk factor for bladder cancer is cigarette smoking, which is responsible for approximately half of all cases. Tobacco smoke contains a range of carcinogenic compounds, including aromatic amines and polycyclic aromatic hydrocarbons, that are excreted in the urine and come into direct contact with the urothelial lining. Studies have consistently shown that current and former smokers have a markedly increased risk of developing bladder cancer compared to never-smokers, and risk escalates with both duration and intensity of exposure [8].

Occupational exposure to carcinogenic substances is another major contributor, particularly in industries involving the production or use of dyes, rubber, leather, textiles, and certain chemicals such as benzidine and 2-naphthylamine. Workers exposed to these substances over long periods have a two- to four-fold increased risk of developing urothelial carcinoma, underscoring the necessity of occupational safety measures and regulatory oversight [9].

Additional risk factors include chronic inflammation and irritation of the bladder, such as that seen in patients with long-term indwelling catheters, chronic urinary tract infections, or bladder stones. In regions endemic for Schistosoma haematobium, chronic infection with this parasite is strongly

10.48047/jocaaa.2024.33.06.107

associated with squamous cell carcinoma of the bladder. Prior pelvic radiation therapy and chemotherapy agents, particularly cyclophosphamide, have also been implicated in increasing the risk of secondary bladder malignancies [10].

Genetic predisposition plays a role in a subset of patients, with family history conferring a higher risk of developing the disease. Polymorphisms in genes involved in carcinogen metabolism, DNA repair, and cell cycle control may modulate individual susceptibility. Furthermore, males are at higher risk than females, possibly due to differences in occupational exposures, hormonal factors, and metabolic enzyme activity. Understanding these risk factors is essential for the development of targeted prevention and screening strategies, especially in high-risk populations [11].

C. The 2022 WHO Classification of Tumors of the Urinary Tract

The 2022 World Health Organization (WHO) classification represents a significant advancement in the pathological understanding and diagnostic stratification of urinary tract tumors, particularly urothelial neoplasms. This edition emphasizes the integration of morphological features with emerging molecular and genetic data to refine diagnostic categories and improve clinical relevance. One of the most impactful updates is the recognition of the diverse spectrum of urothelial carcinoma, which now includes additional variant morphologies and new insights into the molecular underpinnings of tumor progression [12].

Among the major changes is a clearer distinction between non-invasive and invasive lesions, as well as the formal recognition of rare histologic subtypes and precursor lesions. The classification now incorporates updated criteria for grading and staging, reflecting contemporary understanding of tumor biology and clinical behavior. It also highlights the significance of identifying variant histologies, which may be associated with differing prognostic and therapeutic implications. The inclusion of molecular markers, such as FGFR3 and TP53 mutations, is increasingly advocated to aid in subclassification and risk stratification [13].

Importantly, the 2022 WHO classification sets the stage for the adoption of novel biomarkers and ancillary techniques in diagnostic practice. It provides a framework for future research focused on the clinical utility of new molecular targets, including proteins like Prolyl 4-Hydroxylase Beta Polypeptide (P4HB), which may have diagnostic, prognostic, or therapeutic implications. This evolution in classification underscores the dynamic nature of the field and the ongoing pursuit of precision oncology in urothelial carcinoma [14].

D. Pathological Features of Urinary Bladder Carcinoma

The pathological assessment of bladder carcinoma is fundamental to diagnosis, prognostication, and therapeutic decision-making. Urothelial carcinoma most commonly arises from the urothelial lining of

10.48047/jocaaa.2024.33.06.107

the bladder and can present as papillary (exophytic) or non-papillary (flat) lesions. Papillary tumors exhibit slender, branching fibrovascular cores lined by neoplastic urothelium, while flat lesions, such as carcinoma in situ (CIS), are characterized by marked cytological atypia without obvious architectural distortion [15].

Grading of urothelial carcinoma is primarily based on the degree of cytologic and architectural atypia. Low-grade tumors display orderly cellular arrangement, mild nuclear pleomorphism, and rare mitoses, whereas high-grade tumors exhibit disordered architecture, significant nuclear enlargement, hyperchromasia, and frequent mitotic figures. Accurate grading is crucial as high-grade lesions carry a higher risk of invasion, recurrence, and progression compared to low-grade tumors [16].

Staging, determined by the depth of invasion into the bladder wall, remains the single most important prognostic factor. Non-muscle-invasive disease (Ta, T1, Tis) is confined to the mucosa or lamina propria, while muscle-invasive tumors (T2 and above) infiltrate the muscularis propria or beyond. The presence of lymphovascular invasion, perineural invasion, and involvement of adjacent organs further worsens prognosis and influences management strategies. Transurethral resection specimens must be thoroughly sampled to ensure accurate assessment [17].

The tumor microenvironment, including the composition of the stroma, inflammatory infiltrates, and presence of necrosis, also plays a significant role in tumor behavior and response to therapy. Recent research has highlighted the impact of the extracellular matrix and stromal remodeling—processes in which proteins such as P4HB are involved—on tumor progression and metastasis. These findings are gradually being incorporated into routine pathological evaluation to provide more nuanced risk assessment [18].

Immunohistochemistry has emerged as an invaluable adjunct to traditional histopathology, particularly in challenging cases where morphology is equivocal. Markers such as GATA3, p63, cytokeratins, and more recently P4HB, can aid in confirming urothelial origin, distinguishing between variant histologies, and identifying molecular subtypes. This evolving toolbox enables pathologists to deliver more precise and informative diagnoses [19].

E. Invasive Urothelial Carcinoma

Invasive urothelial carcinoma (UC) represents a critical clinical challenge due to its aggressive biological behavior and poor prognosis compared to non-invasive forms. The transition from non-muscle-invasive to muscle-invasive disease signifies a pivotal event associated with a dramatic increase in the risk of metastasis and cancer-specific mortality. Invasive UC is characterized histologically by the penetration of neoplastic cells through the basement membrane into the lamina

10.48047/jocaaa.2024.33.06.107

propria and/or muscularis propria, often accompanied by marked cytological atypia and architectural disorder [20].

The clinical presentation of muscle-invasive bladder cancer frequently involves painless hematuria, but may also include irritative voiding symptoms or pelvic pain in advanced stages. Tumor invasion is often heterogeneous, with areas of conventional UC intermingled with variant histologies, such as micropapillary or plasmacytoid features, that confer additional prognostic significance. The presence of variant differentiation in invasive UC is associated with resistance to conventional therapies and a propensity for early dissemination [21].

Molecular alterations play a central role in the pathogenesis and progression of invasive UC. Genomic studies have identified recurrent mutations in genes such as TP53, RB1, and FGFR3, as well as dysregulation of cell cycle, apoptosis, and chromatin remodeling pathways. Recent data also implicate proteins involved in the endoplasmic reticulum stress response, such as P4HB, in facilitating tumor cell adaptation to hostile microenvironments and promoting invasiveness. These insights provide new avenues for targeted therapies and prognostic biomarker development [22].

The standard management of muscle-invasive bladder cancer includes radical cystectomy with pelvic lymphadenectomy, frequently combined with neoadjuvant or adjuvant chemotherapy. However, outcomes remain suboptimal, with five-year survival rates ranging from 40–60% depending on stage and molecular subtype. Efforts to personalize therapy through the integration of molecular biomarkers and risk-adapted protocols are ongoing and represent a major focus of translational research in this field [23].

The identification of reliable biomarkers to predict treatment response and disease progression in invasive UC remains a pressing need. Markers such as P4HB are being explored for their potential to complement traditional histopathological criteria, offering improved stratification of patients for tailored therapeutic approaches. As our understanding of the molecular landscape of invasive UC deepens, the prospect of precision oncology becomes increasingly attainable [24].

F. Microscopic Variants of Invasive Urothelial Carcinoma

The recognition of microscopic variants of invasive urothelial carcinoma has important clinical and prognostic implications, as these subtypes often demonstrate distinct biological behavior and differential responses to therapy. The 2022 WHO classification enumerates several variant histologies, including micropapillary, nested, plasmacytoid, sarcomatoid, and lymphoepithelioma-like variants, each with unique morphological features and clinical significance [25].

The **micropapillary variant** is characterized by delicate, slender papillary structures often lacking true fibrovascular cores and frequently displaying retraction artifact. This variant is notably aggressive,

10.48047/jocaaa.2024.33.06.107

with a high propensity for lymphovascular invasion and early metastasis, necessitating prompt and often more radical management [26]. The **nested variant** mimics benign proliferative lesions but demonstrates infiltrative small nests of bland-appearing urothelial cells. Despite its deceptively bland cytology, the nested variant behaves aggressively and is associated with poor outcomes [27].

The **plasmacytoid variant** features discohesive tumor cells with eccentric nuclei and abundant eosinophilic cytoplasm, resembling plasma cells. This subtype is notorious for its diffuse growth pattern, high stage at diagnosis, and tendency for peritoneal spread, often leading to delayed detection and limited therapeutic options. Similarly, the **sarcomatoid variant** comprises both epithelial and mesenchymal elements, portending an extremely poor prognosis due to rapid progression and resistance to standard treatments [28].

Variant histologies can coexist with conventional urothelial carcinoma, complicating diagnosis and necessitating the use of ancillary studies such as immunohistochemistry. Some variants, such as lymphoepithelioma-like carcinoma, may exhibit a more favorable prognosis and better response to chemoradiation, underlining the need for accurate histological classification. Emerging evidence suggests that distinct molecular alterations and microenvironmental factors underlie the phenotypic diversity of these variants, with proteins like P4HB potentially contributing to their pathogenesis and behavior [29].

The identification of variant histologies is not merely an academic exercise; it has direct implications for patient management. Clinical guidelines increasingly recommend variant-specific considerations for therapy and follow-up. Research into molecular signatures, including differential expression of P4HB and related proteins, may further refine risk stratification and therapeutic targeting in these complex tumors [30].

G. Prolyl 4-Hydroxylase Subunit Beta (P4HB)

Prolyl 4-hydroxylase subunit beta (P4HB) is a multifunctional protein that serves as the beta subunit of prolyl 4-hydroxylase, a key enzyme involved in collagen biosynthesis. It also acts independently as protein disulfide isomerase (PDI), catalyzing the formation, breakage, and rearrangement of disulfide bonds in the endoplasmic reticulum, thus playing a pivotal role in protein folding and quality control. P4HB is ubiquitously expressed in various tissues, reflecting its fundamental involvement in cellular homeostasis and stress response mechanisms [31].

Beyond its canonical role in collagen maturation, P4HB has been implicated in a diverse array of biological processes relevant to cancer. It is involved in cellular adaptation to hypoxic stress, regulation of redox balance, and modulation of the unfolded protein response. Dysregulation of P4HB expression has been reported in multiple malignancies, where it is often associated with increased tumor cell

10.48047/jocaaa.2024.33.06.107

proliferation, resistance to apoptosis, and enhanced metastatic potential. These findings have spurred interest in the role of P4HB as both a biomarker and a potential therapeutic target in oncology [32].

In the context of the urinary bladder, P4HB's participation in extracellular matrix remodeling and cellular stress adaptation may facilitate tumor invasion and progression. Recent studies have identified overexpression of P4HB in urothelial carcinoma tissues compared to benign urothelium, suggesting a contributory role in the malignant phenotype. Furthermore, functional experiments indicate that silencing or inhibiting P4HB impairs tumor cell viability and invasiveness, highlighting its relevance in bladder cancer biology [33].

The regulation of P4HB expression is complex and influenced by multiple signaling pathways, including hypoxia-inducible factors (HIFs), endoplasmic reticulum stress sensors, and oncogenic transcription factors. This multifaceted regulation positions P4HB at the intersection of several critical cellular processes that underpin tumor development, progression, and therapeutic resistance. As such, ongoing research seeks to elucidate the precise mechanisms by which P4HB modulates cancer pathobiology and to determine its utility as a diagnostic or prognostic marker [34].

H. The Role and Diagnostic Utility of Prolyl 4-Hydroxylase Beta Polypeptide (P4HB) in Urothelial Carcinoma

The interest in P4HB as a biomarker in urothelial carcinoma has increased with growing evidence demonstrating its overexpression in malignant urothelium compared to normal tissue. Immunohistochemical studies have shown that P4HB is frequently upregulated in both non-muscle-invasive and muscle-invasive bladder cancers, with higher levels correlating with advanced pathological stage and tumor grade. This overexpression suggests that P4HB may play a pivotal role in urothelial carcinogenesis, facilitating tumor growth, survival, and invasion [35].

Mechanistically, P4HB contributes to several hallmarks of cancer through its chaperone activity and involvement in protein quality control within the endoplasmic reticulum. In urothelial carcinoma cells, increased P4HB expression enhances resistance to cellular stress and promotes adaptation to hypoxic and nutrient-deprived tumor microenvironments. By regulating the unfolded protein response and redox balance, P4HB supports tumor cell viability under adverse conditions and may foster chemoresistance, a major obstacle in the treatment of advanced bladder cancer [36].

Clinical studies have explored the prognostic significance of P4HB expression in bladder cancer. High P4HB levels are associated with adverse clinicopathological parameters, including muscle invasion, lymphovascular invasion, and the presence of variant histologies. Patients with elevated P4HB expression tend to exhibit higher rates of disease recurrence and progression, and shorter overall

10.48047/jocaaa.2024.33.06.107

survival, independent of traditional histopathological factors. This underscores the potential utility of P4HB as a prognostic biomarker that can augment existing grading and staging systems [37].

Importantly, the integration of P4HB immunohistochemistry into diagnostic workflows may enhance the accuracy of histopathological classification, especially in challenging cases where morphological overlap between urothelial carcinoma and its variants complicates diagnosis. P4HB can be co-utilized with other established markers, such as GATA3 and CK20, to confirm urothelial origin and to identify high-risk subtypes that may benefit from more aggressive management [38].

From a therapeutic standpoint, P4HB presents as an attractive molecular target due to its central role in maintaining protein homeostasis and supporting tumor survival. Experimental inhibition of P4HB in urothelial carcinoma cell lines results in impaired cell proliferation, increased apoptosis, and reduced invasive capacity. These preclinical findings open avenues for the development of novel anti-cancer strategies that exploit P4HB dependency, either as monotherapy or in combination with conventional chemotherapeutic agents [39].

The regulatory mechanisms underlying P4HB overexpression in bladder cancer are an area of active investigation. Hypoxia, a common feature of the tumor microenvironment, upregulates P4HB via the activation of hypoxia-inducible factors (HIF-1α and HIF-2α). Additionally, oncogenic signaling pathways, such as PI3K/AKT/mTOR and MAPK/ERK, have been implicated in the transcriptional and post-translational regulation of P4HB. Understanding these mechanisms may yield insights into the heterogeneous expression patterns observed across different tumor subtypes and may identify potential combination therapy partners [40].

Recent advancements in molecular pathology have enabled the quantification of P4HB expression using multiplex immunofluorescence and digital image analysis, offering objective and reproducible assessment that may be incorporated into routine diagnostic protocols. These technologies also facilitate the evaluation of P4HB in small biopsy samples and cytology specimens, expanding its potential clinical utility to the early detection and surveillance of bladder cancer [41].

There is emerging evidence that P4HB expression interacts with the immune microenvironment of urothelial carcinoma. Tumors with high P4HB expression may display altered immune cell infiltration and a more immunosuppressive milieu, potentially impacting the response to immunotherapies such as checkpoint inhibitors. Ongoing studies aim to clarify the relationship between P4HB status and the efficacy of immune-based treatments, which could guide patient selection and therapeutic decision-making in the era of personalized medicine [42].

Despite these promising findings, several challenges remain before P4HB can be fully integrated into clinical practice. The heterogeneity of expression across different tumor regions and between primary

10.48047/jocaaa.2024.33.06.107

and metastatic sites necessitates standardized protocols for tissue sampling and scoring. Moreover, large-scale, multicenter validation studies are needed to confirm the prognostic and predictive value of P4HB across diverse patient populations and treatment settings [43].

In summary, P4HB emerges as a multifaceted biomarker and potential therapeutic target in urothelial carcinoma. Its diagnostic, prognostic, and possibly predictive roles warrant further exploration through rigorous translational and clinical research. The integration of P4HB assessment into multidisciplinary care pathways may contribute to more precise risk stratification, better patient selection for tailored therapies, and ultimately improved outcomes in bladder cancer [44].

I. Conclusion

The landscape of urothelial carcinoma is marked by significant histopathological and molecular diversity, presenting ongoing challenges in both diagnosis and management. The emergence of molecular chaperones, particularly Prolyl 4-Hydroxylase Beta Polypeptide (P4HB), has provided new insights into the mechanisms underlying tumor progression, invasion, and therapeutic resistance. Evidence now supports the role of P4HB as a promising biomarker in bladder cancer, with its overexpression closely linked to higher tumor grade, muscle invasion, and unfavorable clinical outcomes.

Incorporating P4HB assessment into diagnostic protocols holds potential to improve the accuracy of pathological classification, especially in cases with ambiguous morphology or variant histologies. Its prognostic value can aid in more precise risk stratification and guide individualized treatment decisions. Experimental models further suggest that targeting P4HB could represent a novel approach to therapy, offering hope for improved outcomes in patients with advanced urothelial carcinoma.

Nonetheless, important challenges remain before P4HB can be widely implemented in routine practice. These include the need for standardized immunohistochemical techniques, validation in diverse patient populations, and a deeper understanding of the molecular mechanisms that regulate P4HB expression. Future research should also address its interactions with the tumor microenvironment and evaluate its predictive value in response to both chemotherapy and immunotherapy.

Overall, P4HB represents a bridge between advancing tumor biology and clinical translation in urothelial carcinoma. Ongoing and future studies will be essential to clarify its full clinical utility, ultimately contributing to more personalized and effective management strategies for bladder cancer.

10.48047/jocaaa.2024.33.06.107

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