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REVIEW ARTICLE

Evolving hallmarks in urothelial bladder cancer: unveiling potential biomarkers

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Abstract
Urothelial bladder carcinoma (UBC), the most frequent type (90%) of bladder cancer and the second most common malignancy of the urogenital region, is a relatively well understood type of cancer, with numerous studies concerning pathogenetic pathways, natural history and bladder tumor biology being reported. Despite this, it continues to remain a challenge in the oncology field, mostly due to its relapsing and progressive nature, and to the heterogeneity in the response to cisplatin-containing regimens. Although the formulae based on clinical staging and histopathological parameters are classically used as diagnostic and prognostic tools, they have proven insufficient to characterize the individual biological features and clinical behaviour of the tumours. Understanding the pathobiology of the disease can add important information to these classical criteria, and contribute to accurately predict outcome and individualize therapy for UBC patients. In this line of investigation, we found that tumour angiogenesis and lymphangiogenesis, the process of invasion and metastasis and the energy metabolism reprogramming / tumour microenvironment encompass several potential biomarkers that seem to influence bladder cancer aggressiveness and chemoresistance. We particularly highlight the roles of lymphovascular invasion, and of RKIP, CD147 and MCT1 immunoexpressions, as relevant prognostic and/or predictive biomarkers, and as promising areas of therapeutic intervention, eliciting for the development of additional studies that can validate and further explore these biomarkers.

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PALAVRAS-CHAVE
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Características biológicas do carcinoma urotelial da bexiga: à descoberta de potenciais biomarcadores

Resumo
O carcinoma urotelial da bexiga (CUB), o tipo de cancro mais frequente deste órgão (90%) e o segundo mais comum da região genitourinária, está relativamente bem caracterizado, fundamentado por inúmeros estudos sobre vias patogenéticas, histogénese e biologia tumoral. No entanto, permanece como um desafio na oncologia, principalmente devido à sua elevada taxa de recidiva e progressão, e à heterogeneidade na resposta a tratamentos de quimioterapia contendo cisplatina. As fórmulas baseadas no estadiamento tumoral e em parâmetros histopatológicos, embora geralmente utilizadas como ferramentas de diagnóstico e prognóstico, são insuficientes para caracterizar as propriedades biológicas e o comportamento clínico dos tumores. A compreensão detalhada da patobiologia da doença poderá adicionar informações importantes aos critérios clássicos, e contribuir para uma correta previsão individual do prognóstico e da terapêutica a utilizar nos doentes com CUB. Nesta linha de investigação, o nosso grupo sugere que na angiogénese e na linfangiogénese tumoral, no processo de invasão e metastização e na reprogramação do metabolismo energético / microambiente tumoral estão implicados potenciais biomarcadores que parecem influenciar a agressividade tumoral e a resistência à quimioterapia no CUB. Salienta-se o papel da invasão linfovascular, e da imunoexpressão das moléculas RKIP, CD147 e MCT1, como biomarcadores de prognóstico e/ou preditivos de resposta à terapêutica, e como áreas promissoras de intervenção terapêutica. É urgente desenvolver estudos adicionais que continuem a explorar e, eventualmente, validar as potencialidades destes biomarcadores.

Introduction

Thirteen years ago, Hanahan and Weinberg suggested that, although encompassing variable mechanistic strategies, cancers in general acquire a set of functional biological capabilities during their multistep development. These include sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis.[1] In their recent review, the authors added to their previous model two enabling characteristics and two emerging hallmarks. They considered that genome instability generates the genetic diversity underlying the acquisition of all hallmarks, and that inflammation promotes multiple hallmark functions. Additionally, the establishment of a tumour microenvironment by the malignant cells but also by recruited normal cells importantly contributes to energy metabolism reprogramming and immune destruction evasion in order to effectively support neoplastic proliferation.[2] This molecular knowledge is already being applied into clinical practice, with targeted therapies that interfere with each of the hallmarks being developed and entering in clinical trial phase or, in some cases, being approved for clinical use in treating certain forms of human cancer.[3-5]

In urothelial bladder cancer (UBC) setting, although a reasonable number of biomarkers seem to be prognostically relevant,[6,7] there is a substantial delay in the translation into the clinics, and clinical trials with molecularly targeted agents have been few in number and largely unsuccessful.[8,9] This is probably due to the unique complexity involved in the dual-track pathway of bladder carcinogenesis, which postulates that UBC develops via two distinct but somewhat overlapping pathways, resulting in two main phenotypic variants with different biological behaviours and prognoses.[10] However, areas in which biomarkers may prove valuable are evident, encompassing the three most important risk factors that threaten survival and life quality of bladder cancer patients.[7] First, the majority of UBCs emerge as non-muscle invasive (NMI), low grade, papillary lesions. Due to their high risk of recurrence, current guidelines recommend intense follow-up that classically relies on invasive techniques such as cystoscopy and biopsy, causing significant patient discomfort and implicating substantial costs. Thus, prediction of tumour recurrence through non-invasive methods would be of great value.[11] Second, an important proportion of NMI tumours, such as high grade or carcinoma *in situ* lesions, incur at an increased risk of progression to muscle-invasive (MI) disease. Timely prediction of progression would guide a vigilant surveillance, and would help clinicians to identify patients in need of early, aggressive management, while avoiding over-treatment in others.[12] Third, the risk of metastasis is the main pitfall for MI-UBC patients, and the majority of bladder cancer deaths occur as a consequence of metastatic disease.[13] Although cisplatin-containing chemotherapy is recommended for locally-advanced or metastatic UBC,[14] survival benefits are impaired in up to 50% of the patients due to chemoresistance and patient fragility.[15] In this scenario, robust biomarkers could help to identify circulating or lymph-node occult micrometastases,