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Opinion Article

Pathology of Urothelial Carcinoma at Molecular Level

Arcila Solomon*

Department of Pathology, Houston Methodist Hospital, Houston, Canada

DESCRIPTION

The morphologic and genomic heterogeneity of urothelial carcinoma is defined by the presence of a broad spectrum of histopathologic characteristics and molecular changes. It often exhibits high somatic mutation rates together with significant genomic and transcriptional variability, which is consistent with the variety of its histomorphologic and clinical characteristics. An update on recent developments in the molecular characterization and novel molecular taxonomy of urothelial carcinoma and different histology.

The genetic landscape of UC has been substantially improved by recent developments in molecular biology and next-generation sequencing technology, which have also shed light on the pathophysiology and molecular biology of UC and some of its variants. The prevalence of significant intra- and inter-tumoral heterogeneity, which may be observed at the clinical, morphological, genomic, and transcriptome levels, is one of the key problems in urothelial carcinoma. There are numerous identified UC variant histologies that can either be pure or, more frequently, combined with UC-NOS. These variations have historically been based on well-defined physical characteristics, and more recent molecular research has shed important new light on them.

Both healthy and sick bladders have several somatic mutation clones in the urothelial lining that appears normal. Through a process of clonal expansion, this mutational background creates a "field effect" that is favourable for the development of urothelial carcinoma. As a result, the final invasive disease is composed of multiple clones that share ancestral mutations but also harbour a variety of novel and unique mutations, as was discovered by multi-regions sequencing from the same bladder.

Several molecular subgroups and classification schemes were discovered through the expression profiling of urothelial carcinoma by RNA and/or immunohistochemistry, some of which were connected to prognosis or responsiveness to various treatments. Although there is a substantial amount of overlap between them, different classifications utilized different names for different subgroups. This classification was subsequently developed and enhanced by the TCGA analysis, which further distinguished three subgroups within the luminal subtype as well as a basal-squamous subtype and a unique neural cluster.

The most frequent divergent differentiation in UC is squamous differentiation (SqD), which can be found in up to 30% of high-grade and/or stage illness. In practically all classification schemas, expression profiling studies that included UC with SqD consistently found that this tumour type almost usually clustered with the basal/squamous subtypes. By examining different regions of the same tumor's "urothelial" and "squamous" morphology, two investigations examined intratumoral heterogeneity within UC with SqD. According to their findings, the expression profiles of urothelial areas were occasionally labelled as luminal, whereas squamous areas were typically labelled as basal/squamous.

An uncommon and aggressive form of UC called Plasmacytoid Urothelial Carcinoma (PUC) has a diffuse and infiltrating pattern of discohesive, single, or tiny clusters of tumour cells, typically with little stromal response. Tumor cells often have eccentrically positioned nuclei that superficially resemble plasma cells. Additionally, most tumour cells include intracytoplasmic vacuoles that press against the nucleus and cause it to compress, giving rise to the signet ring cell appearance.

A rare form of UC known as Micropapillary Urothelial Carcinoma (MPUC) has been described as having aggressive clinical behavior. When compared to classic UC, MPUC consistently exhibits higher rates of ERBB2 amplification, which has been linked in some studies to worse outcomes after radical cystectomy.

The molecular pathways underpinning the onset, progression, and heterogeneity of urothelial carcinoma have recently come under the spotlight thanks to developments in molecular biology and genomics. A consensus on a molecular classification system that is appropriate for everyday clinical usage is urgently required. The recently proposed molecular classifications offer additional significant insights into the biology of MIBC. Ideally, this classification will aid in resolving a number of open issues, such as how stable certain genetic subtypes are inside a specific tumour and after treatment.

Correspondence to: Arcila Solomon, Department of Pathology, Houston Methodist Hospital, Houston, Canada; E-mail: solomona@wellan.ca

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