Editorial

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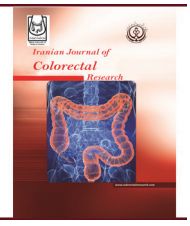

Targeted Immunotherapy Approaches for Intraductal Papillary Neoplasm of the Bile Duct

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Intraductal papillary neoplasm of the bile duct (IPNB) is a specific type of bile duct tumor recognized as a precursor to the development of invasive cholangiocarcinoma. IPNBs are characterized by their unique histological features, including papillary growth patterns within the bile duct lumen, extensive mucin production, and a spectrum of dysplasia ranging from low to high grade. IPNBs are relatively rare, accounting for 5%–15% of all bile duct tumors (1). Clinical manifestations encompass sporadic abdominal pain, episodes of acute cholangitis, and mild to moderate jaundice. A majority of IPNB cases presented with high-grade intraepithelial neoplasia or were associated with an invasive carcinoma. A slight male predilection is observed in patients typically aged between 50 and 70 years (2, 3).

The identification and classification of IPNBs are crucial for clinical management decisions, as their malignant potential and optimal treatment strategies may be different. The accuracy of diagnosis and the effectiveness of treatment for IPNBs have been enhanced due to advancements in diagnostic imaging, endoscopic methods, and the comprehension of genetic and molecular changes associated with these conditions. Furthermore, the precise identification of the distinct features and subclassifications within IPNB holds paramount importance for developing innovative diagnostic and therapeutic approaches. These include advanced targeted therapies, gene therapy, and immunotherapy approaches. Sub-classifications provide critical insights into the underlying pathophysiological mechanisms and variations in clinical outcomes, allowing for tailored treatment strategies (4, 5). According to the Japan Biliary Association and the Korean Association of Hepato-Biliary-Pancreatic Surgery classification, type 1 is characterized by an orderly growth pattern featuring papillary, villous, or tubular structures with consistent thin papillary fibrovascular stalks and substantial mucin production. In contrast, type 2 represents a heterogeneous appearance and irregular growth, incorporating intricate structures such as cribriform and compact tubular patterns. In addition, solid or large cystic components with infrequent mucin overproduction were reported. Notably, almost all type 2 lesions were found to be associated with invasive carcinoma, while type 1 lesions predominantly exhibited low- to high-grade dysplasia (6). Such knowledge enables the development of more targeted and personalized therapies, ultimately leading to enhanced treatment outcomes. Moreover, the delineation of distinct molecular and histopathological subtypes can serve as

a foundation for the exploration of novel therapeutic modalities, such as targeted immunotherapy or gene therapy, for correcting genetic abnormalities associated with particular IPNB subtypes.

The importance of gene mutations and alterations in the genetic profile of IPNB should be considered, particularly in the context of early diagnosis and the development of innovative therapeutic methods, such as targeted therapy. Understanding the specific genetic mutations associated with IPNB is essential for early detection and accurate diagnosis, as these can serve as molecular biomarkers. Furthermore, a comprehensive genetic profile enables predicting the probability of disease progression and the potential for malignancy. Assessment of these genetic alterations is pivotal for the design of targeted therapies that aim to modulate or inhibit the improper signaling pathways associated with these mutations (7, 8). Apart from the genetic profile, the prevalence of IPNB is influenced by geographic variation. These neoplasms are frequently observed in eastern countries, particularly in East Asia (1, 9).

Currently, there are no universally approved mutation patterns identified in all cases of IPNB. However, numerous genetic investigations have explored mutations in single or multiple genes within IPNBs. Although the specific genes affected and their occurrence rates fluctuate across different studies, mainly owing to the limited size of the patient cohorts analyzed. These genetic investigations have unveiled the presence of distinct sets of mutations. These mutations involve a range of genes, including but not limited to *KRAS, GNAS, BRAF, TP53, APC, CTNNB1, ZNRF3, STK11, CDKNZA, PBRM1, ELF3, KMT2C, KMT2D, NF1, PIK3CA, ARID1A, ARID2, BAP1, EPHA6, ERBB2, RNF43*, and *SMAD4* (10-14). On the other hand, a comparison of gene mutations within IPNBs between types 1 and 2 highlights notable differences. For instance, mutations in *KRAS* were remarkably more prevalent in type 1, whereas mutations in *GNAS* and *RNF43* were exclusive to type 1. Conversely, it has been reported that type 2 IPNBs exhibit a frequent mutation in *SMAD4*, *KMT2C*, and *TP53* (15). Based on previous studies, patients with IPNBs had a KRAS mutation frequency of around 18–50% (10, 12, 16). Furthermore, several signaling pathways, such as Ras-MAPK, Wnt/β-catenin, and G protein-coupled receptor (GPCR)/cAMP, have been implicated as central players in the carcinogenesis of IPNBs. The Ras-MAPK pathway, when abnormally activated, can promote uncontrolled cell growth and proliferation, contributing to tumor development (17, 18). The dysregulation of the Wnt/β-catenin pathway can lead to changes in cell differentiation and increased cell division, both of which are crucial factors in IPNB progression (10, 15). Additionally, the GPCR/cAMP signaling pathways have been linked to IPNB carcinogenesis, as they regulate cell signaling and growth (14). Understanding the intricate interactions and disruptions within these signaling pathways provides valuable insights into the molecular mechanisms underpinning IPNB development and progression. In this regard, various trials have been registered on clinicaltrial.gov to evaluate the inhibition of these pathways in gastrointestinal neoplasms with porcupine inhibitors such as CGX1321 (NCT02675946, NCT03507998).

The accurate detection of IPNBs, considering subgroup characteristics, along with the precise identification of molecular alteration and signaling pathway aberrations, might improve the management of this complex biliary neoplasm by paving the way for immune and targeted therapies. Such precision medicine approaches hold the promise of improved therapeutic outcomes with reduced side effects, offering new hope for patients with IPNB and opening the way for more effective and personalized diagnostic and treatment strategies.

Authors' Contribution

MV designed the study. BS and MV reviewed the literature and drafted the manuscript. All authors read and approved the final version and agreed to be accountable for all aspects of the work, including ensuring that any issues about the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest*:* None declared.

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