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Review

Targeting cholangiocarcinoma☆

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ABSTRACT

Cholangiocarcinoma (CCA) represents a diverse group of epithelial cancers associated with the biliary tract, and can best be stratified anatomically into intrahepatic (iCCA), perihilar (pCCA) and distal (dCCA) subsets. Molecular profiling has identified genetic aberrations associated with these anatomic subsets. For example, IDH catalytic site mutations and constitutively active FGFR2 fusion genes are predominantly identified in iCCA, whereas KRAS mutations and PRKACB fusions genes are identified in pCCA and dCCA. Clinical trials targeting these specific driver mutations are in progress. However, The Tumor Genome Atlas (TCGA) marker analysis of CCA also highlights the tremendous molecular heterogeneity of this cancer rendering comprehensive employment of targeted therapies challenging. CCA also display a rich tumor microenvironment which may be easier to target. For example, targeting cancer associated fibroblasts for apoptosis with BH3-mimetics and/or and reversing T-cell exhaustion with immune check point inhibitors may help aid in the treatment of this otherwise devastating malignancy. Combinatorial therapy attacking the tumor microenvironment plus targeted therapy may help advance treatment for CCA. This article is part of a Special Issue entitled: Cholangiocytes in Health and Disease edited by Jesus Banales, Marco Marzioni, Nicholas LaRusso and Peter Jansen.

1. Introduction

Cholangiocarcinoma (CCA) remains one of the most dismal tumors with very limited therapeutic options. CCA that are detected at very early stages can be amendable to resection with curative intent, especially peripherally located intrahepatic CCAs, or can be included in a protocol of neoadjuvant radio-chemotherapy with subsequent liver transplantation for perihilar CCA (pCCA) [1]. For tumors beyond these narrow limitations of curative surgical treatment, no other curative therapeutic options exist. CCA comprises a very heterogeneous group of tumors not only with respect to localization (intrahepatic, extrahepatic, perihilar) and pathological subtypes but also regarding genetic makeup [2,3]. The enormous genetic variability still poses a mayor challenge for effective pharmacological treatment. Current systemic therapy is limited to Gemcitabine plus Cisplatin which remains the standard of care but is palliative and of modest benefit [4]. Two non-mutually exclusive approaches are being pursued to address this therapeutic gap in hepatobiliary neoplasia. First, it is anticipated that detailed genetic analysis will identify driver mutations in subsets of patients which can be targeted. The second approach is based on targeting the rich tumor microenvironment of this cancer. Both approaches will be discussed in detail below.

2. Genetic mutations and therapeutic opportunities

The development of whole genome sequencing has taken the search for therapeutic targets in CCA to a new level. For the first time, targeted and individualized therapeutic approaches to this devastating tumor appear possible. At the same time, next-generation sequencing also reveals the complexity and heterogeneity of the different types of CCA and requires a differentiated discussion of driver mutations and drugable targets in different subtypes of CCA [5,6]. In the first part this review will focus on the most prominent molecular alterations and the observations for therapeutics currently in clinical and pre-clinical trials will be discussed. (See Fig. 1.)

2.1. Cyclin-dependent kinase inhibitor 2A/B (CDKN2A/B)

Mutations of CDKN2, also called $p16^{INK4a}$ have been described in 15–20% of CCA, predominantly pCCA and dCCA. Inactivating

Abbreviations: CCA, Cholangiocarcinoma; iCCA, Intrahepatic CCA; pCCA, Perihilar CCA; dCCA, Distal CCA; CDK, Cyclin dependent kinase; CDKN2A/B, Cyclin-dependent kinase inhibitor 2A/B; PLK2, Polo-like kinase 2; FGF, Fibroblast growth factor; HGF, Hepatocyte growth factor; IDH 1/2, Isocytrate dehydrogenase 1/2; PTP, Protein tyrosine phosphatases; ARIDA1, AT-rich interactive domain-containing protein 1A

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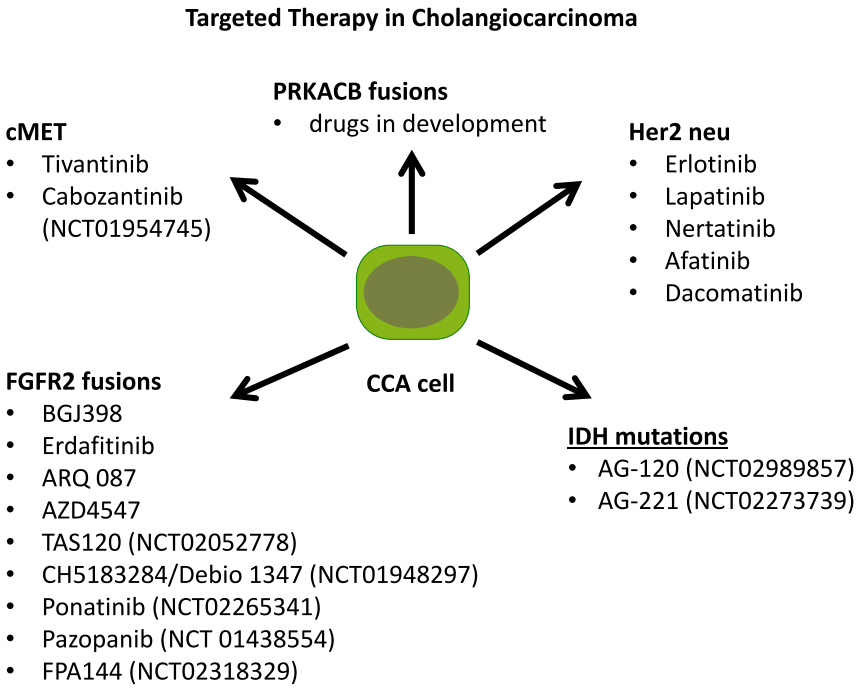

Fig. 1. Summary of some of the most promising tumor cell targeted therapeutic approaches in CCA. Besides the important FGFR2 mutations, mutations in cMET, Her2, IDH and PRKACA/B are promising new targets. Numbers in parenthesis indicate current clinical trials.

mutations result in deregulation of cell cycle control by the INK4 family proteins p16 and $p14^{ARF}$. Mutations or hypermethylation result in loss of S-phase inhibition by p16 or G1 to G2 phase control by $p14^{ARF}$. Focal losses of CDKN2A as well as epigenetic silencing were frequently found in a set of 38 CCA analyzed by the Cancer Genome Atlas Network (TCGN). 47% of the CCA examined showed some loss or mutation of CDKN2 [7]. These data suggest cyclin dependent kinase (CDK) may be beneficial in a subset of CCA. This concept certainly has been overlooked in CCA biology and merits further examination.

2.2. KRAS

As in many malignomas, activating KRAS mutations are frequently detected in all subtypes of CCA and can be found in up to 40% of CCA, predominantly in perihilar and distal CCA [8,9]. Downstream signaling pathways of KRAS include the PI3K-AKT-mTOR as well as the Raf-MEK-ERK axis. Direct therapeutic inhibition of activated KRAS has proven elusive. Instead, inhibition of activated downstream signaling molecules such as MEK, AKT or mTOR is the current therapeutic strategy, as discussed below. Given the intense crosstalk between the signaling pathways downstream of KRAS and possible resistance mechanisms, combination of inhibitors targeting different redundant signaling pathways seems to be the most promising strategy. Co-targeting with a MEK inhibitor and the multi-kinase inhibitor ponatinib for example has shown promising effects in pancreatic cancer cells and in-vivo models [10].

Since there are no direct KRAS inhibitors available today, targeted therapy aims at modulation of downstream signaling along the KRAS pathway. The MEK 1/2 inhibitor selumetinib was evaluated in a phase II trial in advanced biliary tract cancer with perhaps modest effect [11]. Likewise, combination of standard of care Cis/Gem with selumetinib in a phase I trial for patients with advanced biliary tract cancer showed a signal for efficacy while adverse events were acceptable. Further trials targeting the KRAS signaling pathway with MEK inhibitors combined with other therapeutics are ongoing (NCT02042443; NCT01438554).

2.3. mTOR pathway

Several of the common oncogenic mutations in CCA, such as KRAS, MET or FGF converge on the pro-proliferative mTOR signaling pathway. Therefor targeting the mTOR pathway appears as an attractive targeted therapeutic strategy in CCA [12]. Again, redundancy in signaling pathways and signaling crosstalk, particularly with the MEK-ERK pathway makes combination therapies targeting several signaling molecules most promising [13].

Targeting the PI3/AKT/mTOR pathway in human malignancies is a one of the main novel therapeutic approaches. Accordingly, a large number of clinical trials are currently evaluating selective inhibitors [14]. Inhibition of more than one of the signaling molecules is probably necessary to circumvent feedback activation and signaling crosstalk, such as AKT activation by mTOR inhibition [13]. Combination of the mTOR inhibitor everolimus with the standard Cis/Gem did result in stable disease in 6/10 patients with advanced CCA. Current, mTOR inhibitors approved by regulatory agencies for use in man only inhibit the mTOR 1 complex; likely dual mTOR 1 and 2 inhibitors, which are in development, may be more effective for this disease.

2.4. Hedgehog signaling pathway

Activation of the Hedgehog (Hh) signaling pathway has been described in cholangiocarcinoma [15]. Activation of the canonical Hh signaling pathway confers apoptosis resistance in CCA via the cell cycle controlling polo-like kinase 2 (PLK2). Interestingly this pathway depends on intact primary cilia on the cell surfaces. Preclinical studies have shown an antiproliferative effect of the Hh inhibitor cyclopamine with reduction of PLK expression in experimental CCA [16]. In addition to the canonical Hh signaling pathway a non-canonical Hh signaling mechanism has been described particularly in CCA cells which often show a loss of primary cilia. Non-canonical Hh signaling promotes CCA tumor progression and inhibition of this signaling pathway with a specific antagonist to the Hh receptor protein Smoothened resulted in reduced tumor growth and metastasis in a murine model of CCA [17]. Hedgehog signaling inhibitors are approved for use in patients with germ line mutations given rise to basal cell carcinomas [18]. Given the lack of mutations affecting this pathway in CCA, the pharmaceutical industry has been reluctant to invest in testing Hedgehog signaling inhibitors for this disease.